2 Turmeric and Curcumin: From Traditional to Modern Medicine

Maryam Akaberi, Amirhossein Sahebkar, and Seyed Ahmad Emami

Abstract

The rhizome of turmeric (*Curcuma longa* L.) has been used as an herbal medicine, coloring agent, spice, and food additive for thousands of years in different parts of the world particularly in Asian countries. It has been used for a range of diseases in many traditional medical schools, including Islamic traditional medicine, Chinese traditional medicine, and Ayurveda. It has been used mainly for digestive problems, as a cardio-, hepato-, and neuroprotective agent as well as in many inflammatory conditions such as arthritis and for enhancing immune system. Curcumin, a diarylheptanoid derivative found in turmeric, has anti-inflammatory, antioxidant, and anticancer properties; controls obesity and metabolic problems; and improves memory and mood disorders. Therapeutically, curcumin exhibits promising potential in preclinical and clinical studies and is currently in human trials for a variety of conditions, including metabolic syndrome, nonalcoholic fatty liver disease, rheumatoid arthritis, migraine, premenstrual syndrome, ulcerative colitis, knee osteoarthritis, polycystic ovarian syndrome, atherosclerosis, liver cirrhosis, amyotrophic lateral sclerosis, depression, psoriasis, and Alzheimer's disease. Among all beneficial activities reported for curcumin, the research toward the obesity and metabolic-preventing/suppressing aspects of curcumin is growing. These findings emphasize that most of the traditional applications of turmeric is due to the presence of its key constituent, curcumin. According to the traditional background of turmeric use and clinical values of curcumin, further preclinical studies for unstudied properties and clinical studies with larger sample sizes for confirmed activities are expected.

M. Akaberi
Department of Pharmacognosy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

A. Sahebkar (✉)
Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland

Halal Research Center of IRI, FDA, Tehran, Iran
e-mail: sahebkara@mums.ac.ir

S. A. Emami (✉)
Department of Traditional Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
e-mail: emamia@mums.ac.ir

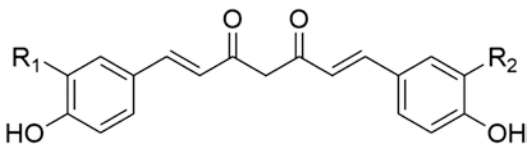
P. C. Guest (ed.), *Studies on Biomarkers and New Targets in Aging Research in Iran*, Advances in Experimental Medicine and Biology 1291, https://doi.org/10.1007/978-3-030-56153-6_2

Keywords

Turmeric · *Curcuma longa* · Zingiberaceae · curcumin · traditional medicine · clinical trials · hepato-protective · cardioprotective · neuroprotective

2.1 Introduction

Turmeric, belonging to Zingiberaceae family, is a perennial plant growing up to one meter high with oblong or cylindrical rhizomes. The rhizomes, being externally brown, consists of an egg-shaped primary rhizome called the "tuber" and several branched secondary rhizomes called the "rhizome." The internal color of the rhizomes ranges from yellow to yellow-orange. This yellow color is due to the presence of pigments known as curcuminoids, which possess diverse pharmacological activities [1]. Chemically, curcuminoids known as diarylheptanoids consist of two aryl groups which are connected to each other via a chain with seven carbons. Curcumin (diferuloylmethane) is the most important bioactive curcuminoids. However, there exist other curcuminoids like desmethoxycurcumin and bisdesmethoxycurcumin in turmeric rhizome (Fig. 2.1) [2]. According to preliminary, preclinical, and clinical studies, the yellow pigment curcumin possesses a worthy pharmacology including anti-inflammatory [3, 4], immunomodulatory [5], antioxidant [6], hypolipidaemic [7], antimicrobial [8], anticarcinogenic [9], antitumor [10, 11, 12], radioprotective [13], neuroprotective [14], hepato-protective [15], nephroprotective [16], cardio-protective [17], and vasoprotective activities. Curcumin has been shown to interact with a wide range of biochemical pathways and influence a variety of molecular targets such as cytokines [18], transcription factors [19], kinases [20], growth factors [21], and microRNAs [22].



Curcuminoids:	R_1	R_2
Curcumin	OCH_3	OCH_3
Desmethoxycurcumin	OCH_3	H
Bisdesmethoxycurcumin	H	H

Fig. 2.1 The chemical structure of the main curcuminoids (the key constituents of turmeric)

Turmeric, also known as Indian saffron, has a long history of use as an herbal medicine, spice, and a coloring agent [23]. The first record of turmeric use dates back to 600 BC in an Assyrian herbal. It was also mentioned by famous Greek physician, Dioscorides, and many traditional scholars in Islamic traditional medicine (ITM) [24–37]. It has also a long-standing reputation in Chinese traditional medicine (TCM), Ayurveda, and different folk medicines around the world [38]. It has been traditionally used for the treatment of a range of diseases including skin disorders (topically) and poor digestion and liver function (internally) [38]. As the knowledge from traditional medicine is a guide for the scientists in the field of natural product–based drug discovery, we decided to investigate the medicinal applications of turmeric in different systems of traditional medicine and the pharmacological activities of curcumin in modern medicine to see the progress from ancient medicine to current clinical trials.

2.2 Traditional View

Turmeric has a long history of medical use in many cultures, particularly in Asia. Turmeric is originally a plant from India and South-East Asia, but nowadays it is cultivated in different regions of the world. However, India is still the largest producer of this valuable plant. Several traditional textbooks [24–37] and electronic scientific literature were searched to find the applications of turmeric in ancient times.

2.2.1 Turmeric in Islamic Traditional Medicine (ITM)

Turmeric, known as Zardchoobeh in Farsi (Persian language) and Hūrd, Kūrkūm, ʿOruqṢūfer, ʿOruqal-ṢabaghinKabir in Arabic, refers to *Curcumalonga* L. [Syn. *C. domestica* Valeton] in ITM textbooks. The latter name has made many of

the ITM scientists a bit confused since *Chelidoniummajus* L. is called ʿOruqal-Ṣabaghin Ṣaghir. Some authors do not distinguish between these two names regardless of the suffixes Kabir or Ṣaghir. Even, some scientists believe that ʿOruqal-Ṣabaghin is the name of *Rubiatinctorum* L.

According to turmeric monographs in the most important textbooks of Islamic medicine, it is deduced that most authors consider it as warm and dry in the second degree and others in the third degree. Pharmacologically, different parts of turmeric plants have been prescribed by ITM physicians to manage various health problems particularly, inflammatory-related disorders. For example, the wood of turmeric has been used for the treatment of toothache. Its extract has been applied for eye problems such as cataract and corneal opacity as well as strengthening eyesight. It was administered topically to relieve the aches in the joints. Putting turmeric powder on wet and infectious wounds can dry them out.Topical administration of turmeric is useful for treating scabies, moist scabies, and herpes. In addition, this spice has been highly recommended for obstructive jaundice (caused by bile duct obstruction), cardiac problems like tachycardia, and nervous system–related problems such as epilepsy and paralysis [24–37].

2.2.2 Indian Traditional Medicine (Ayurveda)

Turmeric is commonly called "Haldi" in north India, and "Manjal" in the south [39]. In India, turmeric is used for a range of diseases similar to ITM. Indian people has used turmeric as a gastric tonic, as well as a blood purifier, digestive, antifever, and wound healing agent. It is also used for pregnancy nausea and skin and liver disease. It has been externally used to relieve conjunctivitis, skin infections, arthritis, hemorrhoids, and eczema. In addition, Indian women apply turmeric on their skin to reduce hair growth [39, 40].

2.2.3 Traditional Chinese Medicine (TCM)

In TCM, a range ofapplications have been reported for turmeric rhizome and tuber. Turmeric rhizomes, being a blood and Qi (vital energy) stimulant, have been used as an analgesic, painkiller, and wound healing agent. It has been prescribed for treating jaundice, chest and abdominal pain and swelling, frozen scapula, postpartum abdominal pain, and amenorrhea. Turmeric tuber, known as Yu Jin, is spicy and bitter and has been used in hot conditions like viral hepatitis since it is considered as a cooling agent. Ithas been used to relieve menstrual pain, heal traumatic injuries, treat enlarged liver cirrhosis, and treat mental problems like mania and epilepsy [41].

2.2.4 Traditional Thai Medicine (TTM)

In TTM, turmeric has been used in cases of gastrointestinal ulcers, anal hemorrhoids, vaginal hemorrhoids, skin diseases, ringworms, and insect bites and for the prevention of gonorrhea and common colds [23].

2.3 Clinical View

The biological and pharmacological effects of curcumin have been described by several in vitro and in vivo studies, showing the potential antioxidant, anti-inflammatory, cardio-protective, anti-microbial, nephro-protective, hepato-protective, hypoglycaemic, immunomodulatory, and anti-rheumatic activities of this valuable compound [37]. Because of potent activities and rare serious side effects of curcumin observed in many preclinical studies, there have been a growing trend in clinical trials on curcumin in the last two decades. A search through scientific databases PubMed and Scopus using the words "curcumin" and "clinical trial" or "trial" yielded a total of 262 articles of which 175 are included in the present paper (Table 2.1). Other articles were systematic reviews, meta-analysis, or irrelevant topics. Similar to in vitro and animal studies, various human trials have shown anti-inflammatory, antioxidant, cardio-protective, antimicrobial properties (especially topically), and tissue protection effects including neuroprotective and hepato-protective activities for curcuminoids (Table 2.1).

Table 2.1 Clinical evidences for biological activities of curcumin

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
1	Analgesic	Postoperative pain after laparoscopic gynecologic surgery	Pilot RCT	60 patients who were to undergo laparoscopic gynecologic surgery	Curcuminoid extract tablets (250 mg) four times a day on postoperative days 1–3 ($n = 30$)	33.1 ± 6.3	↓ Pain severity postoperatively ($p < 0.001$)	[88]
2	Anti-inflammatory	Rheumatoid arthritis (RA)	Double-blind RCT	65 patients with RA	Curcumin nanomicelle capsules (40 mg) 3 times a day for 12 weeks ($n = 30$)	_	Some positive changes in the DAS-28 (disease activity score of 28 joints), TJC (tender joint count), and SJC (swollen joint count), although not significantly	[45]
3	Anti-inflammatory	Migraine	RCT	80 episodic migraine patients	Combination of ω-3 fatty acids (2500 mg) + nano-curcumin (80 mg) over 2 months	_	↓ IL-6 mRNA ↓ hs-CRP serum ($p < 0.05$)	[47]
4	Anti-inflammatory	PMS	RCT	40 women with PMS	Combination of aerobic exercise (for 8 weeks, 3 times in a week) and curcumin capsules (100 mg of curcumin) daily from 7 days before the menstrual period up to 3 first days	18–35	↓ Physical symptoms ($p < 0.05$) ↓ Estrogen levels Improve behavioral and PMS mood symptoms	[89]
5	Anti-inflammatory	Takayasu arteritis (TA)	Double-blind RCT	246 patients with acute TA	Curcumin capsule (300 mg) curcumin daily for 4 weeks	19–52	↓ CRP ↓ TNF-α ↓ ESR (Erythrocyte sedimentation rate) ($p < 0.01$) ↓ BVAS (Birmingham vascular activity score) ($p < 0.05$)	[90]
6	Anti-inflammatory	Mastitisin breastfeeding women	Double-blind RCT	63 breastfeeding women with lactational mastitis	Curcumin topical cream, one pump wvery 8 h for 3 days ($n = 32$)	21–35	↓ Rate of moderate ($p = 0.019$) and mild ($p = 0.002$) mastitis ↓scores for tension ($p < 0.001$), erythema ($p < 0.001$), and pain ($p < 0.001$)	[50]

7	Anti-inflammatory	Radiation dermatitis (RT)	Double-blind RCT	30 breast cancer patients	Curcumin (6 g/d) orally three times per day throughout the course of RT	58.1	↓ Radiation dermatitis severity ($p = 0.008$) ↓ Moist desquamation rate ($p = 0.002$)	[51]
8	Anti-inflammatory	Postmenopausal syndrome	Triple-blind RCT	93 postmenopausal women	Curcumin (500 mg) per day for 8 weeks	51.7	↓ Hot flashes ($p = 0.001$)	[52]
9	Anti-inflammatory	Ulcerative colitis	Double-blind RCT	56 patientswith ulcerative colitis	Curcuminoids nanomicelles (80 mg, three times daily, orally) plus mesalamine (3 g/24 h, orally) for 4 weeks ($n = 28$)	38.2 ± 16.4	↓ Simple clinical colitis activity index	[53]
10	Anti-inflammatory	MeS	Double-blind parallel-group RCT	117 patients with MeS	Curcumin (1 g/day) for 8 weeks ($n = 59$)	44.8 ± 8.7	↓ TNF-α ($p < 0.001$) ↓ IL-6 ($p < 0.001$) ↓ TGF-β ($p < 0.001$) ↓ MCP-1 ($p < 0.001$)	[18]
11	Anti-inflammatory	CPC-SM	Double-blind RCT	89 male subjects	Curcuminoids (500 mg) for 4 weeks ($n = 45$)	51.0 ± 7.3	Improve spirometric parameters FEV1/FVC ($p = 0.002$) ↓ IL-6 ($p < 0.001$) ↓ IL-8 ($p = 0.035$) ↓ TNF-α ($p < 0.001$) ↓ TGF-β ($p < 0.001$) ↓ substance P ($p = 0.016$) ↓ hs-CRP ($p < 0.001$) ↓ CGRP (calcitonin gene-related peptide) ($p < 0.001$) ↓ MCP-1 ($p < 0.001$)	[54]
12	Anti-inflammatory	Obesity	Randomized crossover trial	30 obese individuals	Curcumin (1 g/day) for 4 weeks	18–65	↓ IL-1β ($P = 0.042$) ↓ IL-4 ($P = 0.008$) ↓ VEGF ($P = 0.01$)	[91]
13	Anti-inflammatory	KOA	Pilot double-blind parallel-group RCT	40 patients suffering from knee OA	Curcuminoids (1500 mg/day) for 6 weeks ($n = 19$)	57.3 ± 8.8	↓ WOMAC (Western Ontario and McMaster universities osteoarthritis index) ($p = 0.001$) ↓ VAS ($p < 0.001$) ↓ Lequesne's pain functional index ($p = 0.013$)	[57]

(continued)

Table 2.1 (continued)

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
14	Anti-inflammatory	Solid tumors (ST)	Double-blind RCT	80 subjects with ST	Curcuminoids (180 mg/day) for 8 weeks ($n = 40$)	25–65	↑ QoL ($p < 0.001$) ↓ TNF-α ($p < 0.001$) ↓ TGFβ ($p < 0.001$) ↓ IL-6 ($p = 0.061$) ↓ Substance P ($p = 0.005$) ↓ hs-CRP ($p < 0.001$) ↓ CGRP ($p < 0.001$) ↓ MCP-1 ($p < 0.001$)	[92]
15	Anti-inflammatory	Chronic SM-induced pruritic skin lesions	Double-blind RCT	96 sulfur mustard (SM)-exposed patients	Curcumin (1 g/day) for 4 weeks ($n = 46$)	37–59	↓ IL-8 ($p < 0.001$) ↓ hs-CRP ($p < 0.001$) ↓ CGRP ($p < 0.001$) ↑ QoL	[93]
16	Anti-inflammatory	KOA	Double-blind RCT	44 patients	Diclofenac (75 mg/day) with curcumin (1000 mg/day) for 3 months	_	Decrease pain and improve function in daily living though not significantly	[58]
17	Anti-inflammatory	PMS	Double-blind RCT	70 patients with PMS	Curcumin capsules (100 mg) twice daily for 7 days before menstruation and for 3 days after menstruation for 3 successive cycles ($n = 35$)	25.2 ± 9.2	↓ Total severity of PMS score	[49]
18	Anti-inflammatory, Anti-oxidant	Obesity	Parallel RCT	60 overweight and obese adolescent girls	Curcumin (500 mg/day) + a slight weight loss diet for 10 weeks	13–18	↓ IL-6 ↓TAC (total antioxidant capacity) ↓ MDA ↓ hs-CRP ↓ IL-6	[94]
19	Anti-inflammatory, antioxidant	Infertility in men	Double-blind RCT	60 infertile men	80 mg curcumin nanomicelle daily for 10 weeks ($n = 30$)	20–45	↑ Total sperm count ($p < 0.001$) ↑ Sperm concentration ($p < 0.001$) ↑ Sperm motility ↑ TAC ($p < 0.001$) ↑ MDA ($p < 0.001$) ↑ CRP ↑ TNF-α ($p < 0.01$)	[95]

20	Antioxidant	Polycystic ovarian syndrome (PCOS)	RCT	72 patients with PCOS	Curcumin capsules (1500 mg) 3 times per day for 12 weeks	18–41	↑ Gene expression of PGC1α ($p = 0.011$) ↑ Activity of the Gpx ($p = 0.045$) ↑ Gene expression of SIRT1 ↑ SOD enzymenon-significantly	[61]
21	Antioxidant	β-Thalassemia major	Double-blind RCT	61 patients with β-thalassemia major	Curcumin capsules (500 mg) twice daily for 12 weeks	18–40	↓ Serum MDA ($p = 0.002$), ↓ Total ($p < 0.001$) and direct ($p < 0.001$) bilirubin ↑ TAC ($p = 0.005$)	[96]
22	Antioxidant	CPC-SM	RCT	89 subjects	Curcuminoids (1500 mg/day) in combination with piperine (15 mg/day) for a period of 4 weeks ($n = 45$)	51.0 ± 7.3	↑ Serum GSH, ↓ MDA, Improving COPD assessment test and St. George respiratory questionnaire ($p < 0.001$)	[55]
23	Antioxidant	Type 2 diabetes mellitus (T2DM)	Double-blind RCT	118 patients with T2DM	Curcumin (1000 mg/day) + piperine (10 mg/day) for 8 weeks	18–65	↑ TAC ($p < 0.001$) ↑ SOD activities ($p < 0.001$) ↓ Serum MDA levels ($p < 0.001$)	[97]
24	Antioxidant	KOA	Double-blind RCT	40 patients with KOA	Curcuminoid capsules (1500 mg/day) + piperine (15 mg/day) for 6 weeks ($n = 19$)	57.3 ± 8.8	↑ SOD ($p < 0.001$) ↑ GSH ($p = 0.064$) ↓ MDA ($p = 0.044$)	[98]
25	Antioxidant	CPC-SM	Double-blind RCT	89 patients with CPC-SM	Curcumin (500 mg/day) + piperine (15 mg/day) for 4 weeks ($n = 45$)	51.0 ± 7.3	↑ GSH ↓ MDA Improve COPD assessment test and St. George respiratory questionnaire ($p < 0.001$)	[55]
26	Antioxidant	ST	Double-blind RCT	80 subjects with ST	Curcuminoids (180 mg/day) for 8 weeks ($n = 40$)	25–65	↓ Serum thiobarbituric acid reactive species ($p < 0.001$) ↑ SOD and catalase ↑ GSH ($p < 0.001$) ↑ QoL ($p = 0.003$)	[99]

(continued)

Table 2.1 (continued)

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
27	Antioxidant	SM-induced pruritus	Double-blind RCT	96 male Iranian veterans	Curcumin (1 g/day) for 4 weeks ($n = 46$)	37–59	↓ Substance P ($p < 0.001$) ↓ SOD ($p = 0.02$), ↓ Gpx ($p = 0.006$) and catalase ($p < 0.001$) ↓ Pruritus score ($p < 0.001$) ↓ VAS (visual analogue scale) score ($p < 0.001$) ↓ Overall ($p < 0.001$) and objective SCORAD (scoring atopic dermatitis) ($p = 0.009$) ↓ Dermatology life quality index ($p < 0.001$)	[59]
28	Anti-infective	Oral infections	RCT	27 adults	Photodynamic therapy with blue light and curcumin (30 mg/L)	20–35	↓ CFU (colony-forming units) ($p = 0.001$) ↓ Microbial reduction ($p < 0.05$)	[100]
29	Anti-infective	Chronic periodontitis	RCT	10 patients with two sites in the contralateral quadrants having probing pocket depths of ≥5 mm	Curcumin gel tropically+ SRP (scaling and root planning) for 4 weeks	–	↑ Periodontal parameters ↓ Plaque index ↓ Probing depth	[101]
30	Cardio-protective	Metabolic disorders in PCOS subjects	Double-blind RCT	60 women with PCOS	Curcumin (500 mg/day) for 12 weeks ($n = 30$)	18–40	↓ Weight and BMI ($p = 0.03$) ↓ FBG ($p = 0.002$) ↑ Serum insulin ($p = 0.02$) ↑ Insulin resistance ($p = 0.02$) ↑ Insulin sensitivity ($p = 0.02$) ↓ Total cholesterol ($p = 0.001$) ↓ LDL-cholesterol ($p = 0.001$) ↓ TC/HDL-C ($p < 0.001$) ↑ HDL-C levels ($p = 0.01$) ↑ Gene expression of PPAR-γ ($p = 0.03$) ↑ LDL receptor ($p < 0.001$)	[102]

31	Cardio-protective	PCOS-associated diabetes	Double-blind RCT	60 women with PCOS	1 g turmeric extract 95% (475 mg curcuminoids covering 70–80% curcumin, 15–20% demethoxycurcumin and 2.5–6.5% bisdemethoxycurcumin) daily for 6 weeks	18–40	↑ Serum insulin ($p = 0.020$) ↑ Insulin sensitivity ($p = 0.003$) ↓HOMA-IR ($p = 0.067$)	[103]
32	Cardio-protective	Atherosclerosis	Double-blind RCT	226 patients with T2DM	The extract (250 mg curcuminoids) Three capsules curcumin twice a day for 6 months ($n = 113$)	59.2 ± 1.1	↓ Pulse wave velocity ↑ Serum adiponectin ↓ Leptin	[104]
33	Cardio-protective	Hemodialysis-induced inflammation	Parallel, double-blind RCT	26 hemodialysis patients	Nano-curcumin soft gel three times/day (120 mg/d) over 12 weeks	18–80	↓ hs-CRP ($p < 0.001$) ↓ Serum adhesion molecule VCAM-1 ($p < 0.001$), ↓ TG, TC and LDL-C	[44]
34	Cardio-protective	MeS	Double-blind clinical trial	120 patients with MeS	Curcumin group (CG) (1 g/day), phospholipidated curcumin group (PCG) (1 g/day) for 6 weeks	18–65	↑ Serum Zn in both CG and PCG ($p < 0.001$) though higher in PCG in the ($p < 0.05$) ↑ Serum Zn/Cu level, more significant in PCG ($p < 0.001$)	[105]
35	Cardio-protective	Myocardial injury following elective percutaneous coronary intervention (PCI)	Pilot RCT	110 patients undergoing elective PCI	Single dose of 480 mg nanomicelle curcumin orally and the standard treatment ($n = 55$)	58.6 ± 9.1	↓ The raise of CK-MB (creatine kinase-MB)	[17]
36	Cardio-protective	Cardiovascular risk factors	RCT	60 overweight and obese female	95% turmeric extract tablet (500 mg) per day for 10 weeks	13–18	↓ BMI ($p = 0.019$) ↓ WC ($p = 0.008$) ↓ HC ($p = 0.030$) ↑ HDL ($p = 0.042$) ↓TG/HDL ($p = 0.021$)	[75]
37	Cardio-protective	Diabetes	Double-blind RCT	53 patients with T2DM	Curcumin capsule (1500 mg) 3 times a day for 10 weeks ($n = 25$)	40–70	↓ Mean weight ($p < 0.05$) ↓ BMI ($p < 0.05$) ↓ WC ($p < 0.05$) ↓ FBG ($p < 0.05$)	[106]

(continued)

Table 2.1 (continued)

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
38	Cardio-protective	MeS	Double-blind, placebo-controlled clinical trial	80 overweight subjects with suboptimal values of FPG (fasting plasma glucose)	800 mg phytosomal curcumin (200 mg curcumin, 120 mg phosphatidylserine, 480 mg phosphatidylcholine and 8 mg piperine) twice/day for 8 weeks	18–70	↑ Fasting plasma insulin (FPI) ↑ HOMA index ↓ WC ↓ Blood pressure, TG ↓ Liver transaminases ↓ γ-GT ↓ Liver steatosis index ↓ Serum cortisol	[107]
39	Cardio-protective	β-Thalassemia major	Double-blind RCT	68 patients with β-thalassemia major	Curcumin capsules (500 mg/day) for 12 weeks	26.0 ± 6.9	↓ HOMA-IR ($p = 0.048$) ↓ TG ($p = 0.020$) ↓ TG/HDL-C ratio ($p = 0.024$) ↓ hs-CRP levels ($p = 0.022$)	[108]
40	Cardio-protective	Metabolic disorders in HIV/AIDS subjects	Double-blind, crossover, randomized clinical trial	20 patients with HIV/AIDS under antiretroviral therapy	Curcumin (1000 mg/day) for 30 days	45.5 (9.7)	↓ TG	[109]
41	Cardio-protective	Cardiovascular disease risk factors and arterial function	Double-blinded, placebo-controlled trial	22 obese men	Curcumin (500 mg/day) formulated with fenugreek soluble fiber for 2 weeks	18–35	Improve homocysteine and HDL concentrations	[74]
42	Cardio-protective	Diabetes	Double-blind RCT	44 patients with T2DM	Curcumin (1500 mg/day) for 10 weeks	40–70	↓ hs-CRP ($p < 0.05$) ↑ Adiponectin ($p < 0.05$)	[110]
43	Cardio-protective	Hypercholes-terolemia	Double-blinded, 2 × 2 factorial RCT	76 individuals with hypercholeste-rolemia	Phytosterols (2 g/day) + curcumin (200 mg/day) for 4 weeks	18–70	↑ Cholesterol-lowering effects of phytosterols	[111]
44	Cardio-protective	Hyperlipidemia	Double-blind RCT	118 patients with T2DM	Curcumin (1000 mg/day) + piperine (10 mg/day) for 12 weeks	18–65	↓ TC ($p = 0.023$), non-HDL-C ($p = 0.014$), ↓ lipoprotein(α) [Lp(α)] ($p = 0.001$) ↑ HDL-C ($p = 0.048$)	[112]

45	Cardio-protective	MeS	Pilot, double-blind RCT	127 patients with MeS	Curcumin (1000 mg/day) for 8 weeks ($n = 59$)	44.8 ± 8.7	↑ Adiponectin ($p < 0.001$) ↓ Leptin ($p < 0.001$)	[113]
46	Cardio-protective	Obesity	RCT	44 overweight subjects	800 mg *Curcuma longa* extract (95% curcumin) + 8 mg piperine twice a day for 1 month	39.1 ± 16.8	↑ Weight loss ↑ Body fat ↓ WC ↓ HC ↓ BMI ($p < 0.01$)	[67]
47	Cardio-protective	MeS, dislipidemia	RCT	100 patients with MeS	Curcuminoids (1000 mg/day) for 8 weeks ($n = 50$)	25–75	↓ LDL-C, TC, TG and Lp(α) ↑ HDL-C	[114]
48	Cardio-protective	Hyperlipidemia	Double-blind RCT	65 patients with MeS	Curcumin extract capsules (630 mg thrice daily) for 12 weeks ($n = 33$)	59.0 ± 10.1	↑ HDL-C ($p < 0.05$) ↓ LDL ($p < 0.05$)	[115]
49	Cardio-protective	Diabetes	Double-blind, placebo-controlled trial	100 overweight/obese patients with T2DM	Curcuminoids (300 mg/day) for 3 months ($n = 50$)	55.4 ± 6.4	↓ FBG ($p < 0.01$), ↓ HbA1c ($p = 0.031$), ↓ HOMA-IR ($p < 0.01$) ↓ Total free fatty acid ($p < 0.01$) ↓ TG ($p = 0.018$) ↑ Lipoprotein lipase ($p < 0.01$)	[72]
50	Cardio-protective	Hyperlipidemia	Double-blind RCT	30 obese individuals	Curcumin (1 g/day) for 30 days	15–65	↓ TG ($p = 0.009$)	[116]
51	Hepato-protective	NAFLD	Randomized controlled trial	102 patients with NAFLD (grades 1–3)	Phytosomal form of curcumin (1000 mg/day) for 8 weeks ($n = 50$)	45.0 ± 12.6	↓ BMI ($p = 0.003$) ↓ WC ($p = 0.024$) ↓ AST ($p < 0.001$) ↓ ALT ($p < 0.001$)	[117]
52	Hepato-protective	NAFLD	Double-blind RCT	80 patients with NAFLD	Curcumin formulation (500 mg/day equivalent to 70 mg curcumin) for 8 weeks ($n = 40$)	46.4 ± 11.6	↓ Liver fat content ↓ BMI ↓ TC, LDL-C, TG ↓ ALT, AST ↓ Glucose ↓ Glycated hemoglobin	[118]
53	Hepato-protective	NAFLD	RCT	87 patients with NAFLD (grades 1–3)	1000 mg/day for 8 weeks ($n = 50$)	45.0 ± 12.6	↓ TC ($p < 0.001$) ↓ LDL ($p < 0.001$) ↓ TG ($p < 0.001$) ↓ non-HDL-C ($p < 0.001$) ↓ Uric acid ($p < 0.001$)	[119]

(continued)

Table 2.1 (continued)

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
54	Hepato-protective	Diabetes	Double-blind RCT	100 patients with T2DM	Curcumin (500 mg) and piperine (5 mg) daily for 3 months	18–65	↓ Glucose ($p = 0.048$), ↓ C-peptide ($p < 0.001$) ↓ HbA1c ($p < 0.001$) ↓ ALT ($p = 0.032$) ↓ AST ($p = 0.002$)	[120]
55	Hepato-protective	NAFLD	Double-blind RCT	84 overweight/obese patients with NAFLD	Curcumin capsules (40 mg) twice/day for 3 months ($n = 42$)	25–50	↑ HDL, ↑ Insulin sensitivity ↑ Nesfatin ↓ Fatty liver degree ↓ Liver transaminases ↓ WC, FBS, FBI, HbA1c, TG, TC, LDL, HOMA-IR, TNF-α, hs-CRP, and IL-6 ($p < 0.05$)	[70]
56	Hepato-protective	NAFLD	Double-blind RCT	65 eligible patients	Phospholipidated curcumin capsules (250 mg/day) equivalent to 50 mg/day pure curcumin) for 8 weeks	44.8 (11.14)	↑ HDL-C ($p = 0.01$) ↓ Leptin: adiponectin ratio ($p < 0.001$)	[121]
57	Hepato-protective	Iron deficiency	Double-blind RCT	68 β-thalassemia major patients	Curcumin capsules (500 mg) twice/day for 12 weeks	18–40	Alleviate iron burden and liver dysfunction by: ↓ NTBI (nontransferrin bound iron) ($p = 0.001$) ↓ ALT ($p = 0.018$) ↓ AST ($p = 0.009$)	[122]
58	Hepato-protective	NAFLD	Double blind RCT	80 healthy participants with moderately high BMI (24–30)	Tablets containing a combination of hot water extract of *Curcuma longa* and curcumin thrice a day for 12 weeks	51.7	↓ Serum liver enzyme levels possibly through the suppression of systemic inflammation	[43]
59	Hepato-protective	Liver cirrhosis	Double-blind RCT	70 patients with liver cirrhosis	Curcumin (1000 mg/day) for 12 weeks ($n = 35$)	20–70	Improve quality of life (QoL)	[123]

60	Hepato-protective	NAFLD	Double-blind RCT	55 patients with NAFLD	One capsule containing 500 mg curcuminoids (plus 5 mg piperineper day for 8 weeks	18–70	Improve the severity of NAFLD ($p = 0.002$) Improve serum concentrations of TNF-α ($p = 0.024$), MCP-1 ($p = 0.008$) and EGF ($p = 0.0001$)	[124]
61	Hepato-protective	Liver cirrhosis	Double-blind RCT	70 patients with liver cirrhosis	Curcumin (1000 mg/day) for 3 months ($n = 35$)	20–70	↓ Severity of cirrhosis ↓ MELD(i), MELD, MELD-Na, (model for end-stage liver disease) ↓ Child–Pugh scores ($p < 0.001$)	[125]
62	Hepato-protective	NAFLD	Double-blind RCT	58 NAFLD patients	Phospholipid curcumin (250 mg) per day for 8 weeks	25–65	↓ Some serum metabolites including: 3-methyl-2-oxovaleric acid, 3-hydroxyisobutyrate, kynurenine, succinate, citrate, α-ketoglutarate, methylamine, trimethylamine, hippurate, indoxyl sulfate, chenodeoxycholic acid, taurocholic acid, and lithocholic acid	[126]
63	Neuroprotective	Diabetic sensorimotor polyneuropathy	Parallel, double-blind RCT	80 diabetic patients	80 mg nano-curcumin supplementation for 8 weeks ($n = 40$)	30–60	↓ HbA1c ($p < 0.001$) ↓FBS ($p = 0.004$) ↓ Total score of neuropathy ($p < 0.001$) ↓ Total reflex score ($p = 0.04$) ↓ Temperature ($p = 0.01$)	[127]
64	Neuroprotective	Diabetic peripheral neuropathy (DPN)	Double-blind RCT	80 patients with T2DM and DPN	Nano-curcumin capsules (80 mg) daily for 8 weeks ($n = 40$)	30–60	↓ Mean score of depression (0.02) ↓ Mean score of anxiety ($p = 0.009$)	[128]
65	Neuroprotective	ALS	Double-blind RCT	54 eligible patients with ALS	80 mg nanocurcumin daily for 12 month ($n = 27$)	18–85	↑ Survival curves ($p = 0.036$)	[129]

(continued)

Table 2.1 (continued)

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
66	Neuroprotective	Migraine	Double-blind, phase II RCT	100 men and women with episodic migraine	A combination of nano-curcumin (80 mg) + CoQ10 (300 mg)	32	↓ Frequency, severity, duration of migraine attacks and HDR (headache diary results) ($p < 0.001$) Better scores in migraine-specific questionnaires ($p < 0.001$)	[48]
67	Neuroprotective	Migraine	Placebo-controlled clinical trial	74 episodic migraine patients	ω-3 fatty acids and nano-curcumin for 2 months	–	↓ COX-2/iNOS mRNA and serum levels ↓ Frequency, severity, and duration of headaches ($p < 0.05$)	[46]
68	Neuroprotective	Alzheimer's disease	Double-blind, placebo-controlled trial	40 subjects	Theracurmin® containing 90 mg of curcumin twice daily for 18 months ($n = 21$)	51–84	↑ Memory and attention in non-demented adults ↓ Amyloid and tau accumulation in brain regions	[130]
69	Neuroprotective	ALS	Double-blind therapeutic trial	Patients with ALS	Curcumin (600 mg/day) for 6 months	_	↓ Disease progression ↓ Oxidative damage ↑ Aerobic metabolism	[131]
70	Neuroprotective	PMS	Double-blinded RCT	70 patients with PMS	Curcumin capsules (100 mg) twice daily for 7 days before menstruation and for 3 days after menstruation for 3 successive menstrual cycles ($n = 35$)	25.2 ± 9.2	↑ Serum brain-derived neurotrophic factor levels	[132]
71	Neuroprotective	Depression	Double-blind RCT	50 patients with major depressive disorder	Curcumin extract (500 mg, twice daily) for 8 weeks	18–65	↑ Urinary thromboxane B2 ($p < 0.05$) ↑ Substance P ($p < 0.001$)	[133]

72	Wound healing	Wound and pain associated with episiotomy	Double-blind RCT	120 healthy primiparous women with a vaginal delivery	Topical use of curcumin for 10 days after delivery	–	↓ Total scores of the REEDA ($p < 0.001$)	[134]
73	Wound healing	Aphthous stomatitis	Double blind RCT	57 patients	Curcumin gel (2% curcumin) for 2 weeks ($n = 28$)	18–65	↓ Pain intensity and size of aphthous ulcer	[135]
74	Wound healing	Oral submucous fibrosis (OSMF)	Parallel RCT	60 patients with OSMF	Curcumin tablet (300 mg) twice daily for 6 months ($n = 30$)	17–60	Improvement in mouth opening, burning sensation, tongue protrusion, and cheek flexibility	[136]

2.3.1 Anti-Inflammatory and Antioxidant Activities

The anti-inflammatory activity of curcumin, being reported for the first time in 1971, has been investigated in many preclinical and clinical trials so far [41, 42]. In many cases, curcumin exerts its beneficial activity via decreasing acute or chronic inflammatory responses (Table 2.1). Curcumin inhibits the production of pro-inflammatorymonocyte/macrophage-derived cytokines such as interleukin-8 (IL-8), monocyte inflammatory protein-1(MIP-1), monocyte chemotactic protein-1 (MCP-1), IL-1b, and tumor necrosis factor-α (TNF-α) in several in vitro studies. Also, in vivo studies demonstrated the beneficial effect of curcumin on adipose tissue through the inhibition of several pro–inflammatory mediators, such as MCP-1, IL-1β, TNFα, IL-6, and cyclooxygenase 2 (COX2) [6, 43].

The clinical trials also support the benefit of curcumin in the treatment of acute and chronic inflammatory problems including advanced chronic kidney disease with hemodialysis [19, 44], cardiovascular diseases, rheumatoid arthritis [45], migraine [46–48], premenstrual syndrome (PMS) [49], mastitis [50], radiation dermatitis [51], postmenopausal syndrome [52], ulcerative colitis [53], chronic pulmonary complications of sulfur mustard (CPC-SM) [54, 55], metabolic syndrome (MeS) [56], knee osteoarthritis (KOA) [57, 58], and chronic SM-induced pruritic skin lesions [59] via suppressing the production of cytokines including IL-1β, IL-4, IL-6, IL-8, and TNF-α [60].

The protective effect of curcumin against oxidative damage has been proven in several cell lines and animal models. Curcumin reduces lipid peroxidation through the normalization of antioxidant enzyme levels, such as superoxide dismutase, catalase, and glutathione peroxidase (Gpx). It is a free radical scavenger of hydroxyl (OH) and nitric oxide (NO) radicals, protects DNA against oxidative injury, and reduces reactive oxygen species (ROS). Moreover, it can activate other cellular antioxidants such as heme oxygenase-1, NADPH:quinone oxidoreductase-1 and glutathione, upregulated Nrf2-ARE-regulated pathways [6, 61–63].

A systematic review and meta-analysis of curcumin in the management of inflammatory and oxidative stress markers concluded that there was a significant tendencyin favor of taking curcumin-containing supplements through a significant reduction in IL-6, high sensitive c-reactive protein(hs-CRP), and malondialdehyde (MDA) levels [64]. Another meta-analysis found that consumption of curcumin for 4 weeks or longer may play an antioxidative role by reducing circulating MDA concentrations and increasing superoxide dismutase (SOD) activity and the effect is greater when combined with piperine [65].

2.3.2 Metabolic Disorders

Metabolic disorders have been one of the major health problems in recent decades in both developed and developing countries. Interestingly, many of the studied clinical trials have been focused on investigating the effects of curcumin on different components of metabolic problems [56, 63, 66–69]. Accordingly, most of these studies have shown the beneficial effects of curcumin on regulating glucose and lipid contents of people with MeS or subjects prone to it. In the following paragraphs, the effects of curcumin are discussed in two main categories, namely, its cardio- and hepato-protective activities.

2.3.2.1 Cardio- and Vaso-Protective

Curcumin is gaining growing interest in the scientific community for treating cardiovascular problems. Curcumin has cardio-protective activities through different mechanisms and multiple molecular targets mainly due to its exogenous and endogenous antioxidant capabilities (Table 2.1). In particular, curcumin is involved in the regulation of lipid and glucose metabolism. Therefore, curcumin exerts its cardio-protective activity either through decreasing blood glucose levels via increasing insulin sensitivity and secretion [70–72] and decreasing insulin resistance or by regulating lipid metabolism such as decreasing triglycerides (TG), low density lipoprotein (LDL) and increasing high density lipoprotein

(HDL) levels as well as decreasing obesity risk factors including body mass index (BMI), waist and hip circumferences [63, 73–75]. Curcumin regulates gene expression of PPAR-γ and LDL receptor, decreases serum CRP, adhesion molecule VCAM-1, creatine kinase-MB (CK-MB), leptin and cortisol, and increases serum adiponectin (Table 2.1).

Owing to the extensive clinical studies on curcumin, there are a large number of systematic reviews and meta-analysis from published works. Most of these analyses emphasized on the beneficial effects of curcumin in regulating blood glucose and lipid levels though there are some inconsistencies in the results. For instance, a meta-analysis, published in 2017, included seven double-blind, randomized, controlled trials (n = 649) of curcumin for dyslipidemia. Curcumin significantly reduced serum LDL-C and TG levels as compared to those in the control group though serum HDL-C levels were not obviously improved [76]. A systematic review of the efficacy of curcumin in patients with MeS concluded that curcumin appears to reduceTG, and total cholesterol (TC), as well as fasting glucose levels, homeostasis model of assessment-estimated insulin resistance (HOMA-IR), glycosylated hemoglobin (HbA1c) while no significant effects on HDL and LDL cholesterol levels [77]. A systematic review and meta-analysis of the role of curcumin as an adjunct therapy in patients with MeS found seven clinical trials published up to late 2018. Data analysis showed that curcumin can significantly improve FBG, TG, HDL-C, and diastolic blood pressure levels [56]. In another systematic review studying eleven clinical trials on curcumin given to patients with disglycemia found benefit in improving FBG and HbA1c compared with placebo but not HOMA-IR [71]. A systematic review and meta-analysis of seven clinical trials investigating the effects of curcumin glucose profile in prediabetic patients revealed that curcumin can significantly reduce HbA1c and FBG [78].

In addition to direct effects of curcumin on blood glucose and lipid levels, curcumin appears to increase adiponectin and decrease leptin content. A 2019 systematic review of randomized, double–blind clinical trials identified six studies and concluded that curcumin supplementation significantly increased adiponectin concentrations in comparison with placebo. Greater effects on adiponectin were observed in trials lasting ≤10 weeks [79]. Another systematic review also published in 2019 investigated the influence of curcumin intake on weight loss among patients with MeS and related disorders. Eighteen clinical studies were identified from up to 2018 involving a total of 1604 patients. Curcumin intake significantly reduced BMI, weight, waist circumference (WC), as well as leptin levels and increased adiponectin levels [66].

2.3.2.2 Hepato-Protective

Curcumin has demonstrated promising hepatoprotective activity through decreasing serum liver enzyme levels such as AST (aspartate aminotransferase) and ALT (alanine aminotransferase) [80], improving BMI, WC and hip circumference (HC) [81], decreasing liver fat content [69], and improving serum concentrations of TNF-α, MCP-1 and epidermal growth factor (EGF).

Among the reviewed clinical trials investigating the hepato-protective activities of curcumin, nonalcoholic fatty liver disease (NAFLD) is the most studied disorder. Unfortunately, NAFLD, a major cause of liver-related morbidity, is prevailing due to the rising epidemic of obesity. A systematic review and meta-analysis of curcumin versus placebo in the treatment of NAFLD concluded that curcumin supplementation significantly reduced BMI and WC [73]. Another meta-analysis found that curcumin supplementation in NAFLD patients makes a significant reduction in ALT, AST, serum TC, LDL, FBG, HOMA-IR, serum insulin, and WC [68]. Similarly, a meta-analysis that included 4 RCTs with a total of 229 NAFLD patients found that curcumin decreases LDL-C, TG, fasting blood sugar (FBS), HOMA-IR, weight, and AST levels compared with placebo [69].

2.3.3 Neuroprotective and Antidepressant

Neuroprotective potential of curcumin thought to be largely mediated by antioxidantmechanisms, anti-inflammatory responses such as inhibition of cytokine production [82], and reducing amyloid and tau accumulation in brain regions. Several clinical trials have examined the effects of curcumin supplementation on nervous system–related disorders like age-related cognitive decline, dementia, depression, and mood disorders. As it is shown in Table 2.1, curcumin supplementation has neuroprotective effects in a wide range of diseases including diabetic polyneuropathy, amyotrophic lateral sclerosis (ALS), migraine, Alzheimer's disease, depression, and neurological symptoms associated with PMS.

Among all neuroprotective activities reported for curcumin, the efficacy of curcumin in Alzheimer's disease and depression is receiving considerable research attention. In vitro and in vivo studies show that curcumin can significantly inhibit monoamine oxidase MAO-A and MAO-B activities in a dose-dependent manner, increase serotonin, noradrenaline, and dopamine levels markedly. A recent meta-analysis of six clinical trials with a total of 289 subjects showed that curcumin improved the memory and cognitive function in elderly people [83]. A meta-analysis evaluating the efficacy and safety of curcumin for the treatment of depression concluded a significant effect of curcumin in ameliorating depressive symptoms. Out of all six included trials, significant anti-anxiety effects were observed in 3 of the trials [84]. Another meta-analysis of six clinical trials, up to 2015, on curcumin in patients with major depression found that although there is a significant reduction of depression symptoms in all the patients, curcumin had the highest effect when given to middle-aged patients, for longer duration of administration, and at higher doses [85]. The anti-depressant and anti-anxiety activities of curcumin have also been confirmed by a recent meta-analysis of nine clinical trials [86].

2.3.4 Indications Supported by Both Traditional Medicine and Clinical Trials

From applications of turmeric in different systems of traditional medicine and the observed clinical efficacy and safety of curcumin in several trials, it can be concluded that there is a correlation between the data extracted from both sources. As indicated in the section "traditional view," turmeric is mostly used in inflammatory and oxidative conditions and has been prescribed as a heart, liver, and neurological tonic as well as digestive problems in ITM, TCM, and Ayurveda. Islamic and Chinese traditional medicines and Ayurveda as the ancient schools of medicine have a large contribution to the distribution of old medicine to the modern world. The prescriptions in these schools, mostly being based on phytotherapy, are full of clues to find lead compounds with great medicinal properties. For instance, in ITM like many other medical systems, herbs have provided the basis for solving health problems. In this medical system, considerable respect was paid to the qualities of individual herbs. Physicians were familiar with the nature of each remedy, its actions, energy pattern, indications, and duration of action. Moreover, they were expected to understand the specific relationships of the herbal medicine to the organs, its toxicity contraindications, and antidotes, types of preparation that can be made, its dosage, administration and even its natural habitat. There were many outstanding physicians who made their scientific knowledge about the medicinal herbs written as Materia Medica. Persians ar-Rhazi (Rhazes), al-Majusi (Haly Abbas), and Ibn-Sina (Avicenna) were among the well-known physician who did notable developments. They were not only well familiar with the theoretical aspects of phytotherapy but also in practice [41, 87]. Turmeric is one of the well-known spices and medicinal herbs with many monographs written about its characteristics and medicinal values. It is almost mentioned in all ITM medicinal textbooks [87]. Curcuminoids are the yellow pigments in turmeric. Curcumin is the most important bioactive curcuminoids. As discussed in the previous

sections, there are thousands of articles investigating the pharmacological activities of curcumin. Interestingly, the trend of clinical trials is toward to the claimed traditional uses. In the case of cardiovascular, metabolic, gastrointestinal, and neurological disorders, curcumin shows promising activities. It has also shown beneficial activities in inflammatory conditions and as a chemopreventive agent. Thus, it can be concluded that most of the reported traditional properties of turmeric are because of the presence of curcumin.

Taken together, curcumin is a promising lead compound for therapeutically purposes. Further research projects including in vitro and in vivo studies for the undetermined potential activities of curcumin as well as clinical trials for the potent properties reported in preliminary studies are expected. In addition, for the activities investigated in many human trials with positive results, more comprehensive studies are necessary.

Acknowledgements The authors are grateful to Mashhad University of Medical Sciences (MUMS) for help and supports.

Conflict of Interest: None.

References

1. Moreira J, Saraiva L, Pinto MM, Cidade H (2020) Diarylpentanoids with antitumor activity: a critical review of structure-activity relationship studies. Eur J Med Chem 92:112177. https://doi.org/10.1016/j.ejmech.2020.112177
2. Hatamipour M, Ramezani M, Tabassi SAS, Johnston TP, Sahebkar A (2019) Demethoxycurcumin: a naturally occurring curcumin analogue for treating non-cancerous diseases. J Cell Physiol 234(11):19320–19330
3. Mollazadeh H, Cicero AFG, Blesso CN, Pirro M, Majeed M, Sahebkar A (2019) Immune modulation by curcumin: the role of interleukin-10. Crit Rev Food Sci Nutr 59(1):89–101
4. Hasanzadeh S, Read MI, Bland AR, Majeed M, Jamialahmadi T, Sahebkar A (2020) Curcumin: an inflammasome silencer. Pharmacol Res 159:104921. https://doi.org/10.1016/j.phrs.2020.104921. Epub 2020 May 25. PMID: 32464325
5. Abdollahi E, Momtazi AA, Johnston TP, Sahebkar A (2018) Therapeutic effects of curcumin in inflammatory and immunemediated diseases: a nature-made jack-of-all-trades? J Cell Physiol 233(2):830–848
6. Boroumand N, Samarghandian S, Hashemy SI (2018) Immunomodulatory, anti-inflammatory, and antioxidant effects of curcumin. J Herb Med Pharmacol 7(4):211–219
7. Panahi Y, Ahmadi Y, Teymouri M, Johnston TP, Sahebkar A (2017) Curcumin as a potential candidate for treating hyperlipidemia: A review of cellular and metabolic mechanisms. J Cell Physiol 233(1):141–152. https://doi.org/10.1002/jcp.25756. Epub 2017 Jun 6. PMID: 28012169
8. Naz RK, Lough ML, Barthelmess EK (2016) Curcumin: a novel non-steroidal contraceptive with antimicrobial properties. Front Biosci (Elite Ed) 8(1):113–128
9. Teymouri M, Pirro M, Johnston TP, Sahebkar A (2017) Curcumin as a multifaceted compound against human papilloma virus infection and cervical cancers: A review of chemistry, cellular, molecular, and preclinical features. BioFactors 43(3):331–346.
10. Mohajeri M, Bianconi V, Ávila-Rodriguez MF, Barreto GE, Jamialahmadi T, Pirro M, Sahebkar A (2020) Curcumin: a phytochemical modulator of estrogens and androgens in tumors of the reproductive system. Pharmacol Res 156:104765. https://doi.org/10.1016/j.phrs.2020.104765. Epub 2020 Mar 23. PMID: 32217147
11. Doello K, Ortiz R, Alvarez PJ, Melguizo C, Cabeza L, Prados J (2018) Latest in vitro and in vivo assay, clinical trials and patents in cancer treatment using curcumin: a literature review. Nutr Cancer 70(4):569–578
12. Iranshahi M, Sahebkar A, Hosseini ST, Takasaki M, Konoshima T, Tokuda H (2010) Cancer chemopreventive activity of diversin from Ferula diversivittata in vitro and in vivo. Phytomedicine 17(3-4):269–273. https://doi:10.1016/j.phymed.2009.05.020. Epub 2009 Jul3. PMID: 19577457
13. Kolivand S, Amini P, Saffar H, Rezapoor S, Motevaseli E, Najafi M et al (2019) Evaluating the radioprotective effect of curcumin on rat's heart tissues. Curr Radiopharm 12(1):23–28
14. Forouzanfar F, Read MI, Barreto GE, Sahebkar A (2020) Neuroprotective effects of curcumin through autophagy modulation. IUBMB Life 72(4):652–664
15. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendía LE, Sahebkar A (2017) Efficacy and Safety of Phytosomal Curcumin in Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial. Drug Res (Stuttg) 67(4):244–251. https://doi.org/10.1055/s-0043-100019. Epub 2017 Feb 3. PMID: 28158893.
16. Abd El-Kader M, Taha RI (2020) Comparative nephroprotective effects of curcumin and etoricoxib against cisplatin-induced acute kidney injury in rats. Acta Histochem 122(4):151534. https://doi.org/10.1016/j.acthis.2020.151534
17. Aslanabadi N, Entezari-Maleki T, Rezaee H, Jafarzadeh HR, Vahedpour R (2019) Curcumin for the prevention of myocardial injury following elective percutaneous coronary intervention; a pilot ran-

domized clinical trial. Eur J Pharmacol 858:172471. https://doi.org/10.1016/j.ejphar.2019.172471
18. Saberi-Karimian M, Keshvari M, Ghayour-Mobarhan M, Salehizadeh L, Rahmani S, Behnam B, Jamialahmadi T, Asgary S, Sahebkar A (2020) Effects of curcuminoids on inflammatory status in patients with non-alcoholic fatty liver disease: A randomized controlled trial. Complementary Therapies in Medicine 49, 102322. https://doi.org/10.1016/j.ctim.2020.102322
19. Alvarenga L, Salarolli R, Cardozo LFMF, Santos RS, de Brito JS, Kemp JA, Reis D, de Paiva BR, Stenvinkel P, Lindholm B, Fouque D, Mafra D (2020) Impact of curcumin supplementation on expression of inflammatory transcription factors in hemodialysis patients: a pilot randomized, double-blind, controlled study. Clin Nutr. S0261-5614(20)30110-2. https://doi.org/10.1016/j.clnu.2020.03.007
20. Soltani A, Salmaninejad A, Jalili-Nik M, Soleimani A, Javid H, Hashemy SI et al (2019) 5′-adenosine monophosphate-activated protein kinase: a potential target for disease prevention by curcumin. J Cell Physiol 234(3):2241–2251
21. Saberi-Karimian M, Katsiki N, Caraglia M, Boccellino M, Majeed M, Sahebkar A (2019) Vascular endothelial growth factor: an important molecular target of curcumin. Crit Rev Food Sci Nutr 59(2):299–312
22. Momtazi AA, Derosa G, Maffioli P, Banach M, Sahebkar A (2016) Role of microRNAs in the therapeutic effects of curcumin in non-cancer diseases. Mol Diagn Ther 20(4):335–345
23. Prasad S, Aggarwal BB (2011) Turmeric, the golden spice: from traditional medicine to modern medicine. In: Benzie IFF, Wachtel-Galor S (eds) Herbal medicine: biomolecular and herbal medicine: biomolecular and clinical aspects, 2nd edn. CRC Press/Taylor & Francis, Boca Raton, FL, pp 263–288
24. Rāzi MZ (1968) In: Khān A (ed) Al-Ḥāwi fi'l-Ṭibb (comprehensive book of medicine, in Arabic), vol 31. Osmania Oriental Publications Bureau, Osmania University, Hyderabad
25. Ibn Sinā A (1987) Al-Qānun fi'l-Ṭibb (canon of medicine, in Arabic), vol 2. I.H.M.M.R. Printing Press, New Delhi
26. Herawi M (1967) In: Bahmānyar A (ed) Al-Abniyah an Ḥaqāyeq al-Adwiyah (basics of realities on drugs, in Persian). Tehran University Publications, Tehran, Iran
27. Ibn Jazlah Y (1631) Minhāj al-Bayān fīmā Yastaʿmiluhū al-Insān (in Arabic). League of Arab States, Bulaq, Cairo, Egypt
28. Ibn Beyṭār Z (2001) Al-Jameʿe le-Mofradāt al-Adwiah wal-Aghdhiyah (comprehensive book in simple drugs and foods in Arabic), vol 2. Dār al-Kūtūb al-ʿElmiyah, Beirut, Lebanon
29. Anṭāki D (2000) In: Shams a'ddin A (ed) Tadhkereh Oulūl-albāb (memorandum book, in Arabic). Dār-al-Kūtūb al-ʿElmiyah, Beirut, Lebanon
30. Tonekāboni MM (1959) Toḥfat al-Momenin (rarity of the faithful, in Persian). Mostafavi Press, Tehran, Iran
31. Ghasāni AM (1985) Ḥadiqat al-Azhār fi Māhiyyat al-ʿUshb wa al-ʿUqqār (Flower Garden in the Nature of Herbs and Drugs,in Arabic). Dār al-Gharb al-Islāmi, Beirut, Lebanon
32. Aqili Khorāsāni MH (1992) Makhzan al-Adwiah (Drug Treasure, in Persian). Reprinted from a copy which was printed in Calcutta dated in 1844. Enqelab-e Eslami Publishing and Educational Organization, Tehran, Iran
33. Jorjāni SI (1977) In: Saeedi Sirjani AA (ed) Dhakhireh Khārazmshāhi, (treasure of Khārazmshāh, in Persian), photoprint of the manuscript dated 1206 AD. The lranian Culture Foundation, Tehran, Iran
34. Herawi MY (2008) Baḥr al-Jawāher (Sea of Gems, in Arabic). Institute of Revival of Natural Medicine, Qom
35. Qorashi AA (607-687 AH/1211-1288 AD) al-Shāmel (The comprehensive, in Arabic). Vol. 19. Al Majmaʿ al-Thaqāfi. Abu-Dhabi, United Arab Emirates
36. Jorjāni SI (2006) Al-Aghrāḍ al-Ṭibbia wal Mabāheth al-ʿAlāiia (Medical Purposes and al-Alâee Investigations,in Persian), vol 1. Tehran University Publication, Tehran, Iran
37. Ayati Z, Ramezani M, Amiri MS, Moghadam AT, Rahimi H, Abdollahzade A et al (2019) Ethnobotany, phytochemistry and traditional uses of *Curcuma* spp. and pharmacological profile of two important species (*C. longa* and *C. zedoaria*): a review. Curr Pharm Des 25(8):871–935
38. Vasanthi HR, Parameswari RP (2010) Indian spices for healthy heart - an overview. Curr Cardiol Rev 6(4):274–279
39. Duggi S, Harish H, Handral R, Tulsianand G, Shruthi SD (2013) Turmeric: nature's precious medicine. Asian J Pharm Clin Res 6(3):10–16
40. Samala S, Veeresham C (2017) Ethnobotany of turmeric and its medicinal importance. In: Ethnobotany of India. Volume 3: North-East India and the Andaman and Nicobar Islands. CRC Press/Taylor & Francis, Boca Raton, FL, pp 293–316
41. Bone K, Mills S (2012) Principles and practice of phytotherapy: modern herbal medicine. Principles and practice of phytotherapy, 2nd edn. Elsevier, Austin, TX, pp 900–918
42. Khanna NM (1999) Turmeric – Nature's precious gift. Curr Sci 76(10):1351–1356
43. Kawasaki K, Fukuhara I, Muroyama K, Murosaki S (2017) Effect of a combination of hot water extract of *Curcuma longa* and curcumin on serum liver enzymes, inflammatory markers, and emotional states in healthy participants with moderately high body mass index: a randomized, double-blind, placebo-controlled clinical trial. Jpn Pharmacol Ther 45(2):243–252
44. Vafadar Afshar G, Rasmi Y, Yagmayee P, Khadem-Ansari MH, Makhdomii K, Rasooli J (2020) The

effects of nano-curcumin supplementation on serum level of hs-CRP, adhesion molecules, and lipid profiles in hemodialysis patients, a randomized controlled clinical trial. Iran J Kidney Dis 14(1):52–61
45. Javadi M, Khadem Haghighian H, Goodarzy S, Abbasi M, Nassiri-Asl M (2019) Effect of curcumin nanomicelle on the clinical symptoms of patients with rheumatoid arthritis: a randomized, double-blind, controlled trial. Int J Rheum Dis 22(10):1857–1862
46. Abdolahi M, Jafarieh A, Sarraf P, Sedighiyan M, Yousefi A, Tafakhori A et al (2019) The neuromodulatory effects of ω-3 fatty acids and nano-curcumin on the COX-2/iNOS network in migraines: a clinical trial study from gene expression to clinical symptoms. Endocr Metab Immune Disord Drug Targets 19(6):874–884
47. Abdolahi M, Sarraf P, Javanbakht MH, Honarvar NM, Hatami M, Soveyd N et al (2018) A novel combination of ω-3 fatty acids and nano-curcumin modulates interleukin-6 gene expression and high sensitivity C-reactive protein serum levels in patients with migraine: a randomized clinical trial study. CNS Neurol Disord Drug Targets 17(6):430–438
48. Parohan M, Sarraf P, Javanbakht MH, Foroushani AR, Ranji-Burachaloo S, Djalali M (2019) The synergistic effects of nano-curcumin and coenzyme Q10 supplementation in migraine prophylaxis: a randomized, placebo-controlled, double-blind trial. Nutr Neurosci:1–10. https://doi.org/10.1080/1028415X.2019.1627770
49. 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(3):318–324
50. Afshariani R, Farhadi P, Ghaffarpasand F, Roozbeh J (2014) Effectiveness of topical curcumin for treatment of mastitis in breastfeeding women: a randomized, double-blind, placebo-controlled clinical trial. Oman Med J 29(5):330–334
51. 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(1):34–43
52. Ataei-Almanghadim K, Farshbaf-Khalili A, Ostadrahimi AR, Shaseb E, Mirghafourvand M (2020) The effect of oral capsule of curcumin and vitamin E on the hot flashes and anxiety in postmenopausal women: a triple blind randomised controlled trial. Complement Ther Med 48:102267. https://doi.org/10.1016/j.ctim.2019.102267
53. Masoodi M, Mahdiabadi MA, Mokhtare M, Agah S, Kashani AHF, Rezadoost AM et al (2018) The efficacy of curcuminoids in improvement of ulcerative colitis symptoms and patients' self-reported well-being: a randomized double-blind controlled trial. J Cell Biochem 119(11):9552–9559
54. Panahi Y, Ghanei M, Bashiri S, Hajihashemi A, Sahebkar A (2014) 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 65(11):567–573
55. Panahi Y, Ghanei M, Hajhashemi A, Sahebkar A (2016) Effects of curcuminoids-piperine combination on systemic oxidative stress, clinical symptoms and quality of life in subjects with chronic pulmonary complications due to sulfur mustard: a randomized controlled trial. J Diet Suppl 13(1):93–105
56. Azhdari M, Karandish M, Mansoori A (2019) Metabolic benefits of curcumin supplementation in patients with metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. Phytother Res 33(5):1289–1301
57. Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A (2014) Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. Phytother Res 28(11):1625–1631
58. 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 Thail 95(Suppl 1):S51–S58
59. Panahi Y, Sahebkar A, Amiri M, Davoudi SM, Beiraghdar F, Hoseininejad SL et al (2012) 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(7):1272–1279
60. White CM, Pasupuleti V, Roman YM, Li Y, Hernandez AV (2019) Oral turmeric/curcumin effects on inflammatory markers in chronic inflammatory diseases: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 146:104280. https://doi.org/10.1016/j.phrs.2019.104280
61. Heshmati J, Golab F, Morvaridzadeh M, Potter E, Akbari-Fakhrabadi M, Farsi F et al (2020) The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: a randomized placebo-controlled clinical trial. Diabetes Metab Syndr 14(2):77–82
62. Fleenor BS, Carlini NA, Campbell MS (2019) Curcumin and arterial function in health and disease: impact on oxidative stress and inflammation. Curr Opin Clin Nutr Metab Care 22(6):459–464
63. Jin T (2019) Mechanisms underlying the metabolic beneficial effect of curcumin intervention: beyond anti-inflammation and anti-oxidative stress. Obes Med 13:1–5
64. Tabrizi R, Vakili S, Akbari M, Mirhosseini N, Lankarani KB, Rahimi M et al (2019) The effects of curcumin-containing supplements on biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis of randomized controlled trials. Phytother Res 33(2):253–262
65. Qin S, Huang L, Gong J, Shen S, Huang J, Tang Y et al (2018) Meta-analysis of randomized controlled trials of 4 weeks or longer suggest that curcumin

may afford some protection against oxidative stress. Nutr Res 60:1–12
66. Akbari M, Lankarani KB, Tabrizi R, Ghayour-Mobarhan M, Peymani P, Ferns G et al (2019) The effects of curcumin on weight loss among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol 10:649. https://doi.org/10.3389/fphar.2019.00649
67. Di Pierro F, Bressan A, Ranaldi D, Rapacioli G, Giacomelli L, Bertuccioli A (2015) Potential role of bioavailable curcumin in weight loss and omental adipose tissue decrease: preliminary data of a randomized, controlled trial in overweight people with metabolic syndrome. Eur Rev Med Pharmacol Sci 19(21):4195–4202
68. Jalali M, Mahmoodi M, Mosallanezhad Z, Jalali R, Imanieh MH, Moosavian SP (2020) The effects of curcumin supplementation on liver function, metabolic profile and body composition in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med 48:102283. https://doi.org/10.1016/j.ctim.2019.102283
69. Wei Z, Liu N, Tantai X, Xing X, Xiao C, Chen L et al (2019) The effects of curcumin on the metabolic parameters of non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Hepatol Int 13(3):302–313
70. Jazayeri-Tehrani SA, Rezayat SM, Mansouri S, Qorbani M, Alavian SM, Daneshi-Maskooni M et al (2019) Nano-curcumin improves glucose indices, lipids, inflammation, and Nesfatin in overweight and obese patients with non-alcoholic fatty liver disease (NAFLD): a double-blind randomized placebo-controlled clinical trial. Nutr Metab (Lond) 16:8. https://doi.org/10.1186/s12986-019-0331-1
71. Melo ISVD, Santos AFD, Bueno NB (2018) Curcumin or combined curcuminoids are effective in lowering the fasting blood glucose concentrations of individuals with dysglycemia: systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 128:137–144
72. Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, Meng M et al (2013) Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. Mol Nutr Food Res 57(9):1569–1577
73. Baziar N, Parohan M (2020) The effects of curcumin supplementation on body mass index, body weight, and waist circumference in patients with nonalcoholic fatty liver disease: a systematic review and dose-response meta-analysis of randomized controlled trials. Phytother Res 34(3):464–474
74. Campbell MS, Ouyang A, Krishnakumar IM, Charnigo RJ, Westgate PM, Fleenor BS (2019) Influence of enhanced bioavailable curcumin on obesity-associated cardiovascular disease risk factors and arterial function: a double-blinded, randomized, controlled trial. Nutrition 62:135–139
75. Saraf-Bank S, Ahmadi A, Paknahad Z, Maracy M, Nourian M (2019) Effects of curcumin on cardiovascular risk factors in obese and overweight adolescent girls: a randomized clinical trial. Sao Paulo Med J 137(5):414–422
76. Qin S, Huang L, Gong J, Shen S, Huang J, Ren H et al (2017) Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: a meta-analysis of randomized controlled trials. Nutr J 16(1):68. https://doi.org/10.1186/s12937-017-0293-y
77. Tabrizi R, Vakili S, Lankarani KB, Akbari M, Mirhosseini N, Ghayour-Mobarhan M et al (2018) The effects of curcumin on glycemic control and lipid profiles among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Curr Pharm Des 24(27):3184–3199
78. Poolsup N, Suksomboon N, Kurnianta PDM, Deawjaroen K (2019) Effects of curcumin on glycemic control and lipid profile in prediabetes and type 2 diabetes mellitus: a systematic review and meta-analysis. PLoS One 14(4):e0215840. https://doi.org/10.1371/journal.pone.0215840
79. Clark CCT, Ghaedi E, Arab A, Pourmasoumi M, Hadi A (2019) The effect of curcumin supplementation on circulating adiponectin: a systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Syndr 13(5):2819–2825
80. Goodarzi R, Sabzian K, Shishehbor F, Mansoori A (2019) Does turmeric/curcumin supplementation improve serum alanine aminotransferase and aspartate aminotransferase levels in patients with non-alcoholic fatty liver disease? A systematic review and meta-analysis of randomized controlled trials. Phytother Res 33(3):561–570
81. Mousavi SM, Milajerdi A, Varkaneh HK, Gorjipour MM, Esmaillzadeh A (2020) The effects of curcumin supplementation on body weight, body mass index and waist circumference: a systematic review and dose-response meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr 60(1):171–180
82. Fan C, Song Q, Wang P, Li Y, Yang M, Yu SY (2019) Neuroprotective effects of curcumin on IL-1β-induced neuronal apoptosis and depression-like behaviors caused by chronic stress in rats. Front Cell Neurosci 12:516. https://doi.org/10.3389/fncel.2018.00516
83. Zhu LN, Mei X, Zhang ZG, Xie YP, Lang F (2019) Curcumin intervention for cognitive function in different types of people: a systematic review and meta-analysis. Phytother Res 33(3):524–533
84. Ng QX, Koh SSH, Chan HW, Ho CYX (2017) Clinical use of curcumin in depression: a meta-analysis. J Am Med Dir Assoc 18(6):503–508
85. 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(2):175–183

86. Fusar-Poli L, Vozza L, Gabbiadini A, Vanella A, Concas I, Tinacci S et al (2020) Curcumin for depression: a meta-analysis. Crit Rev Food Sci Nutr 60(15):2643–2653
87. Tayarani-Najaran Z, Tayarani N, Emami SA (2014) The history of islamic medicine at a glance. In: Watson RR, Preedy VR, Zibadi S (eds) Polyphenols in human health and disease. Academic Press, San Diego, CA, pp 17–27
88. Phoolcharoen N, Oranratanaphan S, Ariyasriwatana C, Worasethsin P (2019) Efficacy of curcuminoids for reducing postoperative pain after laparoscopic gynecologic surgery: a pilot randomized trial. J Complement Integr Med 16(4):20180224. https://doi.org/10.1515/jcim-2018-0224
89. Zoodfekr L, Matinhomai H, Tarverdizadeh B (2017) The effect of aerobic exercise and curcumin consumption on clinical signs and serum levels of sexual hormones in 18-35 year-old women with premenstrual syndrome: a randomized clinical trial. Iran J Obstet Gynecol Infertil 20(8):70–79
90. Shao N, Jia H, Li Y, Li J (2017) Curcumin improves treatment outcome of Takayasu arteritis patients by reducing TNF-α: a randomized placebo-controlled double-blind clinical trial. Immunol Res 65(4):969–974
91. 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. https://doi.org/10.1155/2014/898361
92. Panahi Y, Saadat A, Beiraghdar F, Sahebkar A (2014) 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(10):1461–1467
93. Panahi Y, Sahebkar A, Parvin S, Saadat A (2012) A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. Annal Clin Biochem 49(6):580–588
94. Saraf-Bank S, Ahmadi A, Paknahad Z, Maracy M, Nourian M (2019) Effects of curcumin supplementation on markers of inflammation and oxidative stress among healthy overweight and obese girl adolescents: a randomized placebo-controlled clinical trial. Phytother Res 33(8):2015–2022
95. Alizadeh F, Javadi M, Karami AA, Gholaminejad F, Kavianpour M, Haghighian HK (2018) Curcumin nanomicelle improves semen parameters, oxidative stress, inflammatory biomarkers, and reproductive hormones in infertile men: a randomized clinical trial. Phytother Res 32(3):514–521
96. Nasseri E, Mohammadi E, Tamaddoni A, Qujeq D, Zayeri F, Zand H (2017) Benefits of curcumin supplementation on antioxidant status in β-thalassemia major patients: a double-blind randomized controlled clinical trial. Ann Nutr Metab 71(3–4):136–144
97. Panahi Y, Khalili N, Sahebi E, Namazi S, Karimian MS, Majeed M et al (2017) Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial. Inflammopharmacology 25(1):25–31
98. Panahi Y, Alishiri GH, Parvin S, Sahebkar A (2016) Mitigation of systemic oxidative stress by curcuminoids in osteoarthritis: results of a randomized controlled trial. J Diet Suppl 13(2):209–220
99. Panahi Y, Saadat A, Beiraghdar F, Hosseini Nouzari SM, Jalalian HR, Sahebkar A (2014) Antioxidant effects of bioavailability-enhanced curcuminoids in patients with solid tumors: a randomized double-blind placebo-controlled trial. J Funct Foods 6(1):615–622
100. Leite DPV, Paolillo FR, Parmesano TN, Fontana CR, Bagnato VS (2014) Effects of photodynamic therapy with blue light and curcumin as mouth rinse for oral disinfection: a randomized controlled trial. Photomed Laser Surg 32(11):627–632
101. Raghava KV, Sistla KP, Narayan SJ, Yadalam U, Bose A, Mitra K (2019) Efficacy of curcumin as an adjunct to scaling and root planing in chronic periodontitis patients: a randomized controlled clinical trial. J Contemp Dent Pract 20(7):842–846
102. Jamilian M, Foroozanfard F, Kavossian E, Aghadavod E, Shafabakhsh R, Hoseini A et al (2020) Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Nutr ESPEN 36:128–133
103. Sohaei S, Amani R, Tarrahi MJ, Ghasemi-Tehrani H (2019) The effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in overweight/obese women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled clinical trial. Complement Ther Med 47:102201. https://doi.org/10.1016/j.ctim.2019.102201
104. 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(2):144–150
105. Safarian H, Parizadeh SMR, Saberi-Karimain M, Darroudi S, Javandoost A, Mohammadi F et al (2019) The effect of curcumin on serum copper and zinc and Zn/cu ratio in individuals with metabolic syndrome: a double-blind clinical trial. J Diet Suppl 16(6):625–634
106. Hodaei H, Adibian M, Nikpayam O, Hedayati M, Sohrab G (2019) The effect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes: a randomized, double-blind clinical trial. Diabetol Metab Syndr 11:41. https://doi.org/10.1186/s13098-019-0437-7
107. Cicero AFG, Sahebkar A, Fogacci F, Bove M, Giovannini M, Borghi C (2020) Effects of phytosomal curcumin on anthropometric parameters,

insulin resistance, cortisolemia and non-alcoholic fatty liver disease indices: a double-blind, placebo-controlled clinical trial. Eur J Nutr 59(2):477–483
108. Tamaddoni A, Nasseri E, Mohammadi E, Qujeq D, Zayeri F, Zand H et al (2019) A double-blind randomized controlled trial of curcumin for improvement in glycemic status, lipid profile and systemic inflammation in β-thalassemia major. J Herb Med 21:100324. https://doi.org/10.1016/j.hermed.2019.100324
109. SilvaTAL MDC, Medeiros G, Medeiros R, de Souza AJ, Medeiros JA et al (2019) Influence of curcumin supplementation on metabolic and lipid parameters of people living with HIV/AIDS: a randomized controlled trial. BMC Complement Altern Med 19(1):202. https://doi.org/10.1186/s12906-019-2620-7
110. Adibian M, Hodaei H, Nikpayam O, Sohrab G, Hekmatdoost A, Hedayati M (2019) The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Phytother Res 33(5):1374–1383
111. Ferguson JJA, Stojanovski E, MacDonald-Wicks L, Garg ML (2018) Curcumin potentiates cholesterol-lowering effects of phytosterols in hypercholesterolaemic individuals. A randomised controlled trial. Metabolism 82:22–35
112. Panahi Y, Khalili N, Sahebi E, Namazi S, Reiner Ž, Majeed M et al (2017) Curcuminoids modify lipid profile in type 2 diabetes mellitus: a randomized controlled trial. Complement Ther Med 33:1–5
113. Panahi Y, Hosseini MS, Khalili N, Naimi E, Soflaei SS, Majeed M et al (2016) Effects of supplementation with curcumin on serum adipokine concentrations: a randomized controlled trial. Nutrition 32(10):1116–1122
114. Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A (2014) 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(5):851–857
115. 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(12):1770–1777
116. 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(3):374–379
117. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendía LE, Sahebkar A (2017) Efficacy and safety of phytosomal curcumin in non-alcoholic fatty liver disease: a randomized controlled trial. Drug Res (Stuttg) 67(4):244–251
118. Rahmani S, Asgary S, Askari G, Keshvari M, Hatamipour M, Feizi A et al (2016) Treatment of non-alcoholic fatty liver disease with curcumin: a randomized placebo-controlled trial. Phytother Res 30(9):1540–1548
119. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendía LE, Sahebkar A (2016) Curcumin lowers serum lipids and uric acid in subjects with nonalcoholic fatty liver disease: a randomized controlled trial. J Cardiovasc Pharmacol 68(3):223–229
120. Panahi Y, Khalili N, Sahebi E, Namazi S, Simental-Mendía LE, Majeed M et al (2018) Effects of curcuminoids plus piperine on glycemic, hepatic and inflammatory biomarkers in patients with type 2 diabetes mellitus: a randomized double-blind placebo-controlled trial. Drug Res (Stuttg) 68(7):403–409
121. Mirhafez SR, Farimani AR, Dehhabe M, Bidkhori M, Hariri M, Ghouchani BF et al (2019) Effect of phytosomal curcumin on circulating levels of adiponectin and leptin in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. J Gastrointestin Liver Dis 28:183–189
122. Mohammadi E, Tamaddoni A, Qujeq D, Nasseri E, Zayeri F, Zand H et al (2018) An investigation of the effects of curcumin on iron overload, hepcidin level, and liver function in β-thalassemia major patients: a double-blind randomized controlled clinical trial. Phytother Res 32(9):1828–1835
123. Nouri-Vaskeh M, Afshan H, Malek Mahdavi A, Alizadeh L, Fan X, Zarei M (2020) Curcumin ameliorates health-related quality of life in patients with liver cirrhosis: a randomized, double-blind placebo-controlled trial. Complement Ther Med 49:102351. https://doi.org/10.1016/j.ctim.2020.102351
124. Sabery Karimian M, Keshvari M, Ghayour-Mobarhan M, Salehizadeh L, Rahmani S, Behnam B et al (2020) Effects of curcuminoids on inflammatory status in patients with non-alcoholic fatty liver disease: an exploratory randomized controlled trial. Complement Ther Med 49:102322. https://doi.org/10.1016/j.ctim.2020.102322
125. Nouri-Vaskeh M, Malek Mahdavi A, Afshan H, Alizadeh L, Zarei M (2020) Effect of curcumin supplementation on disease severity in patients with liver cirrhosis: a randomized controlled trial. Phytother Res 34(6):1446–1454
126. Chashmniam S, Mirhafez SR, Dehabeh M, Hariri M, Azimi Nezhad M, Nobakht MGBF (2019) A pilot study of the effect of phospholipid curcumin on serum metabolomic profile in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. Eur J Clin Nutr 73(9):1224–1235
127. Asadi S, Gholami MS, Siassi F, Qorbani M, Khamoshian K, Sotoudeh G (2019) Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus: a randomized double-blind placebo-controlled clinical trial. Complement Ther Med 43:253–260

128. Asadi S, Gholami MS, Siassi F, Qorbani M, Sotoudeh G (2019) Beneficial effects of nano-curcumin supplement on depression and anxiety in diabetic patients with peripheral neuropathy: a randomized, double-blind, placebo-controlled clinical trial. Phytother Res 34(4):896–903
129. Ahmadi M, Agah E, Nafissi S, Jaafari MR, Harirchian MH, Sarraf P et al (2018) Safety and efficacy of nanocurcumin as add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a pilot randomized clinical trial. Neurotherapeutics 15(2):430–438
130. Small GW, Siddarth P, Li Z, Miller KJ, Ercoli L, Emerson ND et al (2018) Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: a double-blind, placebo-controlled 18-month trial. Am J Geriatr Psychiatry 26(3):266–277
131. Chico L, Ienco EC, Bisordi C, Lo Gerfo A, Petrozzi L, Petrucci A et al (2018) Amyotrophic lateral sclerosis and oxidative stress: a double-blind therapeutic trial after curcumin supplementation. CNS Neurol Disord Drug Targets 17(10):767–779
132. Fanaei H, Khayat S, Kasaeian A, Javadimehr M (2016) Effect of curcumin on serum brain-derived neurotrophic factor levels in women with premenstrual syndrome: a randomized, double-blind, placebo-controlled trial. Neuropeptides 56:25–31
133. Lopresti AL, Maes M, Meddens MJM, 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(1):38–50
134. Esmaeili Vardanjani SA, Sehati Shafai F, Mohebi P, Deyhimi M, Delazar A, Ghojazadeh M et al (2012) Wound healing benefits of curcumin for perineal repair after episiotomy: results of an Iranian randomized controlled trial. Life Sci J 9(4):5536–5541
135. Manifar S, Obwaller A, Gharehgozloo A, Boorboor Shirazi Kordi HR, Akhondzadeh S (2012) Curcumin gel in the treatment of minor aphthous ulcer: a randomized, placebo- controlled trial. J Med Plants 11(41):40–45
136. Piyush P, Mahajan A, Singh K, Ghosh S, Gupta S (2019) Comparison of therapeutic response of lycopene and curcumin in oral submucous fibrosis: a randomized controlled trial. Oral Dis 25(1):73–79