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Review article

The therapeutic potential of curcumin: A review of clinical trials

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ABSTRACT

Curcuma longa L., its derived extracts and even its major compound curcumin has a long history of use and doubtless effectiveness, reported through increasingly detailed *in vitro, ex vivo, in vivo* and even clinical trials. Regarding its biological effects, multiple health-promoting, disease-preventing and even treatment attributes has been remarkably highlighted. Clinical trials, although have increased in a progressive manner, significant disproportionalities have been stated in terms of biological effects assessment. In this sense, the present report aims to provide an extensive overview to curcumin therapeutic effects in human subjects. For that, clinical trials assessing the curcumin effect on inflammation, skin, eye, central nervous system, respiratory, cardiovascular, gastrointestinal, urogenital and metabolic disorders are here presented and discussed. A special emphasis was also given to curcumin activity on intoxications and multiple malignant diseases.

Contents

1. Introduction 528
2. Clinical trials on curcumin therapeutic effects 529
 2.1. Anti-inflammatory activity of curcumin 529
 2.2. Curcumin and skin diseases 529
 2.3. Curcumin and eye diseases 529
 2.4. Central nervous system diseases 530
  2.4.1. Alzheimer's disease 530
  2.4.2. Déjérine-sottas disease 533
  2.4.3. Depression and anxiety 533
 2.5. Curcumin and respiratory diseases 533
 2.6. Curcumin in cardiovascular protection 533
 2.7. Curcumin and gastrointestinal diseases 533

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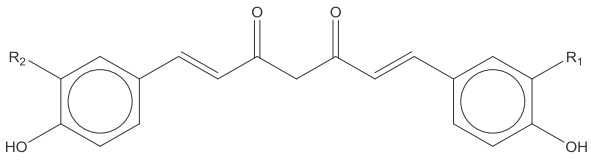
2.8. Curcumin and liver diseases 536
2.9. Curcumin and genitourinary tract diseases 536
2.10. Curcumin and metabolic disorders 537
2.10.1. Curcumin and diabetes 537
2.10.2. Curcumin and obesity 537
2.10.3. Curcumin and β-thalessemia 539
2.10.4. Curcumin and acquired immunodeficiency syndrome (AIDS) 539
2.11. Toxin neutralizing effects of curcumin 539
2.12. Curcumin and cancer treatment 539
3. Conclusions and future perspectives 541
Author contributions 541
Conflicts of interest 542
Acknowledgements 542
References 542

1. Introduction

Curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) are collectively known as curcuminoids [1]. These yellow colored curcuminoids (Fig. 1) are isolated from *Curcuma longa* L. (turmeric) rhizomes, a plant species belonging to Zingiberaceae family [2,3]. Turmeric is a plant known by its medicinal use, dating back to 4000 years ago in the Vedic culture in India, where it was used as a culinary spice and had some religious significance. In herbal and traditional medicine, turmeric is used for rheumatoid arthritis, chronic anterior uveitis, conjunctivitis, skin cancer, small pox, chicken pox, wound healing, urinary tract infections, and liver ailments, strengthening the overall energy of the body, dispelling worms, regulating menstruation, dissolving gallstones, cleansing wounds, and even for various digestive disorders, among other conditions [4]. *C. longa* has on its chemical composition more than 3% curcumin, 1.4% DMC and 1.2% BDMC [5].

The curcumin IUPAC name is (1E, 6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta- 1,6-diene-3,5-dione, also having the following synonyms: 1,7-Bis(4-hydroxy-3- methoxyphenyl)-1,6-heptadiene-3,5-dione or diferuloylmethane, CAS number: 458-37-7 [5], UNII: IT942ZTH98 [6], Drugbank id: DB11672 [7], Einecs: 207-280-5 [8] and PubChem CID: 969516 [9].

Payton et al. [10] studied the typical representation of curcumin as a beta-diketone structure and confirms that it exhibits keto-enol tautomerism. As the main characteristics, this molecule has a molecular formula $C_{21}H_{20}O_6$, molecular weight: 368.385 g/mol, melting point: 179–182 °C, specific gravity: 0.9348 at 15 °C, a log Kow of 3.29 (est) and appears as orange-yellow needles/crystalline powder. Apart from these, curcumin has: 1) a variable solubility, i.e., insoluble in cold water and ether, soluble in alcohol and glacial acetic acid, and very soluble in ethanol and acetic acid; 2) a good stability under recommended storage conditions (−20 °C); and 3) a



Compound	R1	R2
Curcumin	OMe	OMe
Demethoxycurcumin	H	OMe
Bisdemethoxycurcumin	H	H

Fig. 1. Chemical structure of the most common curcuminoids.

hazardous decomposition process under fire conditions, leading to the formation of toxic products (carbon oxides). Almeida et al. [11] also reported the physicochemical properties of curcuminoids. In the same line, Kurien et al. [12] reported the solubility of curcumin for which Aggarwal [13] has commented with bioavailability information. Concomitantly, Modasiya [14] investigated the curcumin solubility in polymers, while Bernabé-Pineda et al. [15] measured the acidity constants in an aqueous solution, and the constant rate for curcumin decomposition. Still, Jager et al. [16] compared curcuminoids' absorption in different formulations, and Prasad et al. [17] reviewed the pharmacokinetic parameters of curcumin, namely those related with delivery, bioavailability, absorption, and metabolism. The main concern with respect to curcumin, when exploiting its biological activity, is its bioavailability due to poor solubility, coupled with its poor absorption in plasma and tissues, rapid metabolism and excretion [18], despite acting as a potent acid-base and boron indicator [19].

On the other hand, and taking a look at curcumin biological effects, this molecule was able of allowing survival in pretreated rats before bleeding [20]. Similarly, Jayaprakasha et al. [21] evaluating the antioxidant activity of individual curcuminoids, stated that the observed effect seemed to be correlated with wound healing speeding-up [22]. In addition, according to Literat et al. [23] curcumin also shows a strong inhibitory action on pro-inflammatory cytokines production. Not least interesting to highlight is that Patočka [24] documented to curcumin a marked anti-amyloidogenic activity, where curiously β-amyloid protein is one of the main targets in Alzheimer's disease treatment. Indeed, a plenty of clinical trials have revealed curcumin' pharmacological properties. For example, Krup et al. [25] and Nasri et al. [26] reviewing the medicinal uses of curcumin, have reported remarkable benefits in the gastrointestinal, respiratory and cardiovascular system, and prominent anti-inflammatory, antidiabetic, hepatoprotective, neuroprotective, chemoprotective, anticancer, anti-allergic and anti-dermatophytic effects, being also able to prevent drug resistance. Velayudhan et al. [27] also documented the traditional use of curcumin, and pointed out that even a single oral dose of up to 8000 mg was not found in the serum. Thus, curcumin is increasingly being conceived as one of the biomolecules to be administer over long-term without any adverse effect [28]. In addition, Hatcher et al. [29] reviewed curcumin' chemopreventive, chemotherapeutic, chemosensitizing, radiosensitization and radioprotective effects. Shen [30] also investigated the curcumin regulatory effects on gut microbiota and observed that this molecule significantly affected its final concentration. Furthermore, curcumin also showed a prominent protective effect on bone density disorders, such as osteopenia [31], osteoarthritis [32], while

helping to relieve pain and swelling in mouth, gingivitis and periodontitis [33].

Indeed, it has been increasingly highlighted that curcumin is able to modulate multiple cell signaling pathways and protect against hepatic conditions, chronic arsenic exposure, and even alcohol intoxication [34]. The most important signaling pathways studied in molecular biology are Sonic Hedgehog, Janus kinase/signal transducers and activators of transcription (JAK-STAT), nuclear factor kappa B (NF-κB), protein kinase B (AKT or PKB) and transforming growth factor β (TGF-β) [35]. For instance, curcumin induces apoptosis by inhibiting *p*-AKT [36] and insulin growth factor 2 (IGF2) [37] in AKT pathway, by inhibiting Sonic Hedgehog leading to apoptosis [38], at same time that suppress dendritic cells activation [39], induces apoptosis in JAK-STAT [40], inhibits NF-κB [41,42], down-regulate TGF-β [43,44] and inhibits mammalian target of rapamycin (mTOR) signaling pathway in the treatment of spinal cord injury [45].

Thus, based on this data, the present report aims to provide an extensive overview to clinical trials assessing the pharmacological effects of curcumin, namely highlighting its therapeutic ability on inflammatory, skin, eye, central nervous system, respiratory, cardiovascular, gastrointestinal, urogenital and metabolic disorders. A special emphasis was still given to its prominent ability to solve human intoxications and even on malignant diseases treatment.

2. Clinical trials on curcumin therapeutic effects

2.1. Anti-inflammatory activity of curcumin

Curcumin is well-known for its anti-inflammatory potential, and many clinical studies have been done to evaluate its bioactive effects in various inflammatory conditions. One of the most frequently investigated condition is arthritis, a chronic disease typically characterized by joints inflammation, which results in joint damage and disability. Dysregulation of inflammatory cytokines [interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)], as well as of chemokines and inflammatory enzymes [matrix metalloproteinase (MMP-9), cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX)] have been closely linked to development of this disease [46–52]. Clinical trials about anti-inflammatory efficacy of curcumin were mostly done on osteoarthritis (OA) and rheumatoid arthritis (RA) patients, where anti-arthritic effect of curcumin has been confirmed [46–52].

The therapeutic effects after oral curcumin administration, in different doses (200–2000 mg/day), formulations (C3 complex, Meriva, NR–INF–02 or mixture with other plant extracts) and time of administration (2 weeks–6 months) were monitored through using distinct symptoms scales evaluation and/or inflammatory and stress markers (Table 1). The first clinical study carried out by Deodhar et al. [46] showed a comparable effect of curcumin with phenylbutazone, on morning stiffness, joint swelling and walking time of RA patients, but none affected grip strength, joint index, and erythrocyte sedimentation rate (ESR). Another study performed in RA patients [49] investigated the effects of curcumin and diclofenac sodium, alone and in combination. It was reported that the group receiving both compounds had the best improvement in either Disease Activity Score (DAS) and American College of Rheumatology (ACR) score. Anyway, clinical trials involving OA patients are more numerous, where, in all cases, significant improvements have been observed for pain, motor capacity, as also for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne's pain functional index (LPFI), Visual Analog Scale (VAS), quality of life (QoL) and Clinicians Global Impression of Change (CGIC) scores [47,51–55]. Similarly, a group of trials monitored the effects of curcumin on inflammatory and stress markers/mediators in OA patients (Table 1) [48,50,55]. These studies found that curcumin administration reduced the inflammatory markers IL-1β, IL-6, soluble CD40 ligand [sCD40L], soluble vascular cell adhesion molecule [sVCAM]-1, and ESR [48], decreased COX-2 enzyme secretion [50] and reduced the levels of systemic inflammation-involved mediators, such as tumor necrosis factor (TNF-α), transforming growth factor-β (TGFβ), IL-6, substance P, high-sensitivity C-reactive protein (hs-CRP), calcitonin gene-related peptide (CGRP) and monocyte chemotactic protein-1 (MCP-1) [55]. Another study aiming to confirm the anti-inflammatory potential of oral curcumin intake in type II Diabetes Mellitus (T2DM) patients, observed a significant improvement in endothelial function, malondialdehyde (MDA), ET-1, IL-6 and TNF-α levels in curcumin-treated group. Satoskar et al. [56] investigated the anti-inflammatory effect of curcumin compared to phenylbutazone or placebo in postoperative patients. Intensity score (TIS) for spermatic cord edema and tenderness, operative site pain and tenderness decreased in curcumin-treated group, triggering a reduction in all inflammatory parameters. In patients with metabolic diseases, a significant reduction in serum cytokines (TNF-a, IL-6, TGF-b and MCP-1) levels, after curcumin supplementation was also recorded [57]. Thus, all these results strongly support curcumin' application in the treatment of various inflammatory conditions.

2.2. Curcumin and skin diseases

Several clinical trials have demonstrated the efficacy of curcumin administration in resolving symptoms associated with vitiligo [58], psoriasis [59–62], pruritis [63], and radiation-induced dermatitis [64] (Table 2). The study by Asawanonda and Khalan [58] in patients with vitiligo reported a pronounced improvement in repigmentation in the group receiving topical curcuminoids therapy along with narrowband UVB (NB-UVB) standard therapy. Concerning to psoriasis, a chronic inflammatory and hyperproliferative skin disorder, four different studies investigated the effect of oral curcumin administration [59,62], in the form of tonic preparation [60] or ointment [61]. The first of all, carried out by Heng et al. [61], concluded that curcumin ointment reduced PhK (serin/threonine-specific protein kinase) activity and keratinocyte transferrin receptor (TRR) expression, reduced parakeratosis severity and epidermal $CD8^+$ cells density. In the following two studies, in which the effect of oral curcumin application was assessed in psoriasis patients, a low response rate was observed: only two of the twelve patients showed improvement [62]. On the other hand, when combined with topical steroids, orally administered curcumin reduced Psoriasis Area and Severity Index (PASI) scores [59]. Finally, recent findings reported by Bahraini et al. [60] highlight that turmeric tonic can improve psoriasis symptoms, measured through using PASI and Dermatology Life Quality Index (DLQI) scores. In addition, a study by Panahi et al. [63], made in patients suffering from cutaneous pruritis induced by chronic sulfur mustard, found a marked decrease in inflammation after oral curcumin supplementation. In these patients, reduced levels of various inflammatory markers, including IL-8, hs-CRP and CGRP were stated after 4 weeks of curcumin intake.

2.3. Curcumin and eye diseases

Clinical trials on the subject of curcumin effect to various ophthalmological disorders demonstrated high efficacy of this compound, when either locally or systemically applied, by oral intake (Table 3). It has been reported that 15-day eye drops application containing turmeric can improve symptoms of conjunctivitis, conjunctival xerosis (dry eye), acute dacryocystitis, degenerative conditions (pterygium or pinguecula) and of

Table 1
Clinical trials on anti-inflammatory activity of curcumin.

Adverse effects, toxicity	Effect of curcumin	Treatment, dose and formulation of curcumin	Trial Length	Number of patients/ Study design	Reference
No	Improvement of morning stiffness, walking time and joint swelling; antirheumatic activity comparable to that of phenylbutazone	Daily dose of either curcumin (1200 mg) or phenylbutazone (300 mg)	2 weeks	18 patients with RA; double blind, crossover study	[46]
No	TIS decreased by 84.2% vs 86% and 61.8% in phenylbutazone and placebo group, respectively; Curcumin reduced all studied inflammatory parameters	Curcumin capsule (400 mg), phenylobutazone (100 mg) alone or placebo-lactose (250 mg), 3 times/ day	6 days	46 male postoperative patients	[56]
No	Significant drop in pain and disability score severity	Herbomineral formulation, containing *Withania somnifera* roots, *Boswellia serrata* stems, *Curcuma longa* rhizomes and a zinc complex (Articulin-F)	6 months	42 patients with OA; double-blind, placebo-controlled, cross-over study	[47]
No	Improvement in endothelial function and MDA, ET-1, IL-6 and TNF-α levels	NCB-02 (standardized preparation of C3 curcuminoid, 300 mg/day), atorvastatin (10 mg/day) or placebo	8 weeks	72 T2DM patients, randomized, parallel-group, placebo-controlled study	[132]
No	Improvement in pain (walking, stairs, and functions of knee) assessed by time spent during 100 m walking and going-up and down a flight of stairs	*C. domestica* extract (2000 mg/day)	6 weeks	107 primary knee OA patients; randomized controlled study	[51]
No	Significant reduction of inflammation markers (IL-1β, IL-6, sCD40L, sVCAM-1) and ESR	Tablets Meriva [curcuminoid mixture (20%), phosphatidylcholine (40%), microcrystalline cellulose (40%)], twice/day, corresponding to 200 mg of curcumin/day	8 months	100 OA patients	[48]
No	Decreased COX-2 secretion	Curcuminoid (30 mg/3 times daily) or diclofenac sodium (25 mg/3 times daily)	4 weeks	80 knee OA patients; randomized open-end blinded evaluation (PROBE) study	[50]
NI	improvements in the pain and function in daily life categories, but no significant difference were observed between the curcumin and control groups	diclofenac at 75 mg/day with Curcumin at 1000 mg/day (equivalent to 250 mg of curcuminoids)	3 months	44 patients with primary knee OA; double-blind prospective randomized control trial	[52]
No	Reduction in DAS, tenderness and swelling of joint scores. Curcumin group showed the highest improvement percentage in overall DAS and ACR scores	Curcumin capsule (500 mg) and diclofenac sodium (50 mg) alone or their combination	8 weeks	45 RA patients; randomized, single-blinded, pilot study	[49]
No	Decreased VAS, WOMAC and CGIC scores	NR–INF–02 (500 mg/twice daily) or glucosamine sulphate (750 mg/ twice daily) alone or in combination	42 days	120 primary knee OA patients; randomized, single blind, placebo-controlled trial	[54]
No	WOMAC (total, pain, function) scores were not significantly different in comparison to ibuprofen; decreased in systemic oxidative stress	Ibuprofen (1200 mg/day) or *C. domestica* ethanolic extracts (1500 mg/day)	4 weeks	367 primary knee OA patients; randomized multicenter study	[53]
No	Greater reductions in WOMAC, VAS and LPFI scores; significant improvement in pain and physical function scores	Capsules containing 500 mg C3 complex (95% curcuminoids) plus 5 mg bioperine (1500 mg/day)	6 weeks	40 mild-to-moderate knee OA patients; pilot randomized double-blind placebo-control parallel-group clinical trial	[55]
No	Significant improvement in QoL score; reduced TNF-α, TGF-β, IL-6, substance P, hs-CRP, CGRP and MCP-1 levels in curcuminoids vs placebo group	Capsules containing 500 mg C3 Complex (95% curcuminoids) plus 5 mg bioperine (1500 mg/day)	8 weeks	80 patients; randomized double-blind placebo-controlled parallel trial	[55]
No	Significant decrease in serum cytokine (TNF-a, IL-6, TGF-β and MCP-1) levels, following curcumin supplementation	Capsules containing 500 mg C3 Complex (95% curcuminoids) plus 5 mg bioperine (1000 mg/day)	8 weeks	117 metabolic syndrome patients, randomized controlled trial	[57]

Legend: ACR, American College of Rheumatology score; CGIC, Clinicians Global Impression of Change; CGRP, calcitonin gene-related peptide; COX-2, cyclooxygenase-2; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; hs-CRP high-sensitivity C-reactive protein; IL, interleukin; IL-6, interleukin 6; LPFI, Lequesne's pain functional index; MCP-1, monocyte chemotactic protein-1; OA, osteoarthritis; RA, rheumatoid arthritis; sCD40L, soluble CD40 ligand; sVCAM-1, soluble vascular cell adhesion molecule 1; TIS, Intensity score for spermatic cord edema and tenderness; T2DM, type II diabetes mellitus; TGF-β transforming growth factor-β; TNF-α, tumor necrosis factor alpha; VAS, Visual Analog Scale, QoL, quality of life; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

postoperative cataract patients [65]. Studies on patients with uveitis demonstrated a marked symptoms improvement in all treated patients [66] and reduced eye discomfort and number of relapses [67] after oral curcumin intake for 12 weeks and 18 months, respectively. Also, a significant improvement was observed in patients with central serous chorioretinopathy after oral curcumin administration [68].

2.4. Central nervous system diseases

2.4.1. Alzheimer's disease

The first clinical trials investigating the effect of curcumin on

Table 2
Clinical trials on the effects of curcumin on skin disorders.

Adverse effects, toxicity	Effect of curcumin	Treatment, dose and formulation of curcumin	Trial Length	Number of patients/Study design	Reference
Radiation dermatitis					
No	RDS scores were reduced in comparison to placebo group	Capsule (curcuminoids C3 complex: curcumin 390 mg, desmethoxycurcumin 75 mg, bisdesmothoxycurcumin 12.5 mg), 6 g/day, *per os*, combined with radiotherapy	Throughout entire course of radiotherapy	30 breast cancer patients, receiving radiation therapy; randomized, double blind, placebo-controlled trial	[64]
Pruritis					
No	Reduced substance P, and SOD, RBC GSH-Px and CTL activities in curcumin group; significant reduction in pruritus severity	Curcumin C3 Complex capsules (Sami Labs Limited) containing 500 mg curcuminoids plus 5 mg bioperine (1000 mg/day)	4 weeks	96 patients, randomized double-blind placebo-controlled parallel trial	[63]
Psoriasis					
NI	Decreased PhK activity in curcumin treated psoriasis, keratinocyte TRR expression, severity of parakeratosis and density of epidermal $CD8^+$ T cells	Ointment, alcoholic gel preparation containing 1% curcumin	4 weeks	30 psoriasis patients, 10 healthy subjects	[61]
No	Low response rate, both (2/12) responders achieved a PASI 75	4500 mg/day of oral Curcuminoid C3 complex®	12 weeks	12 psoriasis patients, phase II, open-label, Simon's two-stage trial	[62]
NI	Higher PASI values reduction in group treated with steroids + curcuminoids, reduced IL-22 level in serum	Topical steroids combined with oral curcumin Meriva (2000 mg/day)	12 weeks	63 patients; randomized, double-blind, placebo-controlled	[59]
NI	Reduced erythema, scaling and induration of lesions (PASI score); improved patients' QoL	Turmeric tonic, twice a day	9 weeks	40 scalp psoriasis patients; randomized, double-blind, placebo-controlled, prospective clinical trial with two parallel groups	[60]
Vitiligo					
No	Repigmentation of lesions	Targeted narrow band UVB + topical tetrahydrocurcuminoid cream	12 weeks	10 vitiligo patients, randomized controlled study	[58]

Legend: SOD, superoxide dismutase; RDS, radiation dermatitis severity; RBC GSH-Px, glutathione peroxidase; CTL, catalase; PhK, serin/threonine-specific protein kinase; TRR, keratinocyte transferrin receptor; PASI, Psoriasis Area and Severity Index; IL-22, Interleukin-22; QoL, quality of life.

Table 3
Clinical trials on the effects of curcumin on eye disorders.

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Length	Number of patients/Study design	Reference
Various ophthalmic disorders					
NI	Improvement in symptoms of most patients	Herbal eye drops preparation (Ophthacare), 2 drops, 4 times daily	15 days	100 patients suffering various ophthalmic disorders, multicentre clinical trial	[65]
Uveitis					
No	Disease improvement (100%) in curcumin group	Capsules of curcumin (1125 mg/day) alone or in combination with antitubercular therapy	12 weeks	53 chronic anterior uveitis patients	[66]
No	Reduced the number of relapses after 1-year treatment and eye discomfort in 80% of patients	Norflo (Meriva) capsules 600 mg, twice/day	12–18 months	106 uveitis patients, non-placebo-controlled study	[67]
Chorioretinopathy					
No	Improvement of visual acuity, reduction in neuroretinal or retinal pigment epithelium detachment	Meriva 1.2 g/day, representing a daily curcuminoid intake of 240 mg	12 months	12 central serous chorioretinopathy patients	[68]

Alzheimer's disease patients showed no such promising results, where no significant difference was observed between the curcumin and placebo group [69,70] after 6 and 12 months of oral administration (Table 4). However, in the study performed by Baum et al. [69], a marked increase in plasma vitamin E and of serum Aβ40 levels were found in treated patients. Indeed, increased Aβ40 levels in serum implied that curcumin can disaggregate Aβ-deposits in the brain, leading to their consequent release into circulation [69]. In addition, the low curcumin efficacy towards dementia symptoms was recently reported by Rainey-Smith et al. [71], where an oral intake of 1500 mg/day for 12 months could not affect clinical measures nor cognitive measures of treated individuals. On the other hand, the study carried out by Hishikawa et al. [72], done on very modest number of AD subjects (3 patients), stated significant improvements in Neuropsychiatric Inventory (NPI) scores after 12 weeks with 100 mg/day curcumin treatment. Recent findings, where novel curcumin formulations (Longvida® and Theracurmin) were optimized to ensure a higher bioavailability, even given in much lower doses (80–180 mg/day), demonstrated both good acute and chronic activities [73,74]. For

Table 4
Clinical trials on the effects of curcumin on central nervous system disorders.

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Length	Number of patients/Study design	Reference
Alzheimer disease					
No	No differences in MMSE scores between curcumin and placebo; increased plasma Aβ40 levels	Capsules or powder (4 g/1 g/0 g) of curcumin, once daily combined with 1 capsule (120 mg) of standardized ginkgo leaf extract	6 months	34 AD patients; double-blind, placebo-controlled, randomized trial	[69]
No	NPI scores decreased significantly in both symptoms of acuity and burden of caregivers	Turmeric powder capsules	3 months	3 patients, case study	[72]
No	No differences observed between treatment groups in clinical (ADAS-Cog, NPI, ADCS-ADL, MMSE) or biomarker efficacy measures	Oral administration of Curcumin C3 Complex®, 0 mg/1000 mg/2000 mg/day. For weeks 24 through 48, subjects that were receiving curcumin continued with the same dose, while subjects previously receiving placebo were randomized in a 1:1 ratio to 2 g/day or 4 g/day.	12 months	36 AD patients; a randomized, double blind, placebo-controlled study with an open-label extension	[70]
No	Acute (1 and 3 h after a single dose) administration increased sustained attention performance and working memory tasks, while chronic (4 weeks) resulted with better working memory and mood; acute-on-chronic (1 and 3 h after single dose following chronic treatment) application improved alertness and contentedness; total and LDL cholesterol levels decreased	Longvida® Optimized Curcumin, in dose of 400 mg (corresponding to 80 mg curcumin in a solid lipid formulation)	1 month	60 healthy older subjects; randomized, double-bind, placebo controlled, phase 3/4 trial	[73]
No	No differences were observed in all clinical as also for cognitive measures	BCM-95®CG (Biocurcumax™), standardized extract of *C. longa* (88% curcuminoids and 7% volatile oil); 1500 mg/day	12 months	160 healthy older adults; randomized, double-bind, placebo-controlled trial	[71]
NI	SRT consistent long-term retrieval, SRT total, visual memory and attention improved with curcumin; decreased FDDNP binding in the amygdala	Theracurmin (containing 90 mg of curcumin) twice daily (180 mg curcumin/day)	18 months	46 patients; randomized, double-blind, two-group parallel design	[74]
Déjérine-Sottas disease					
No	Increased knee flexion and foot strength, improved quality of life	1500 mg/day for the first 4 months, 2500 mg/day during remaining 8 months	12 months	1 patient; dose-escalation safety trial	[75]
Anxiety and depression					
No	More rapid depressive symptoms relief	500 mg/day curcumin or placebo together with antidepressants (escitalopram or venlafaxine)	5 weeks	40 patients with first episode of depression; double-blind, randomized, placebo-controlled study	[80]
No	Responders measured by HAM-D17 scale were higher in the combination group (77.8%) than in fluoxetine (64.7%) and curcumin (62.5%) groups	Fluoxetine (20 mg) and curcumin (1000 mg) individually or in combination	6 weeks	60 MDD patients	[81]
No	From 4 to 8 weeks, curcumin improved several mood-related symptoms, demonstrated by a significant group × time interaction for IDS-SR30 total score and IDS-SR30 mood score, but did not affect STAI score	Curcumin extract (1000 mg/day)	8 weeks	56 MDD patients; randomized, double-blind, placebo-controlled study	[77]
No	Reduced BAI, but no changes in BDI scales	C3 Complex® formula (1000 mg/day) combined with bioperine® (5 mg)	30 days	30 obese subjects; double blind, cross-over trial	[79]
No	HADS and BDI scores were reduced in curcuminoid group	Standard anti-depressive therapy + curcuminoids-piperine combination (1000-10 mg/day) or standard anti-depressive therapy alone	6 weeks	111 MDD patients	[133]
No	Significant antidepressant behavioral response; increased plasma BDNF levels and decreased IL-1β and TNFα levels and salivary COR concentrations	Capsules containing 1000 mg of curcumin [curcumin (70%), demethoxycurcumin (20%), and double demethoxycurcumin (10%)] or placebo	6 weeks	108 male adults; randomized, double-blind, placebo-controlled study	[78]
No	Increased urinary TXB2, substance P, baseline plasma ET-1 and leptin; greater reductions were found in IDS-SR30 score	Curcumin extract (1000 mg/day)	8 weeks	50 MDD patients, randomized, double-blind, placebo-controlled study	[76]

Legend: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory II; BDNF, Brain-derived neurotrophic factor; COR, cortisol; ET-1, plasma endothelin-1; FDDNP, 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene) malononitrile; HADS, Hospital Anxiety and Depression Scale; HAM-D17, Hamilton Depression Rating Scale; IDS, Inventory of Depressive Symptomatology; IL-1β, interleukin 1β; MDD, major depressive disorder; MMSE, Mini–Mental State Examination; NPI, Neuropshychiatric Inventory scores; STAI, State-Trait Anxiety Inventory; SRT, Buschke Selective Reminding Test; TNFα, tumor necrosis factor alpha; TXB2, Thromboxane B2.

instance, in the study by Cox et al. [73], Longvida® improved sustained attention and working memory tasks immediately after a single dose, while after 4-week administration enhanced memory, mood, alertness and contentedness.

2.4.2. Déjérine-sottas disease

The study carried out by Burns et al. [75], where curcumin was administered for 12 months in two escalating doses (1500 and 2500 mg/day), in one patient, a marked improvement in knee flexion and foot strength, as well as in overall QoL was observed. On the other hand, strength of hand and elbow decreased, while pulmonary function and upper/lower extremity disability measures remained unchanged, or were reduced. Further studies including a higher number of patients should be done to confirm the beneficial effects of curcumin to this neuropathologic condition.

2.4.3. Depression and anxiety

The impact of curcumin oral administration on depression has been evaluated through several clinical trials (Table 4). In these studies, curcumin was given orally at doses ranging from 500 to 1000 mg daily, alone [76–78], with bioperine [57,79] or in combination with standard anti-depressive agents escitalopram, venlafaxine or fluoxetine [80,81]. In all trials, the studied individuals evidenced a marked improvement in depression-related symptoms, assessed through using relevant scales. Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Hamilton Depression Rating scale (HAM-D17), Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory II (BDI-II) scores, IDS-SR30 total score and IDS-SR30 score were the most commonly applied. The only exception was the trial carried out by Esmaily et al. [79], where curcumin administration reduced anxiety, but not depression, which might be a consequence of the shortest administration time (30 days vs. 5–8 weeks in other studies). In two additional trials, together with symptoms scales, blood stress parameters and other clinical biomarkers were measured. It was found that curcumin decreased IL-1β and TNFα levels, increased plasma BDNF and decreased salivary cortisol levels [78] in curcumin-treated group, while Lopresti et al. [76] stated a significant increase in urinary thromboxane B2, substance P, baseline plasma endothelin-1 and leptin, considered crucial molecular markers that can be related to the antidepressant mechanism of action of curcumin.

2.5. Curcumin and respiratory diseases

Curcumin has been increasingly investigated for clinical and immunologic purposes (Table 5). For example, in a study developed by Zuccotti et al. [82], the impact of oral curcumin supplementation together with lactoferrin in healthy children with recurrent respiratory tract infections was assessed. The authors found that this combination provides beneficial effects, since significant modulation of immune response was observed in treated children [82].

2.6. Curcumin in cardiovascular protection

An increasing number of clinical trials have demonstrated the cardioprotective efficacy of curcumin intake, mainly attributed to its antihyperlipidemic and anti-atherosclerotic effects (Table 6). These studies highlighted that oral curcumin administration in doses varying from 20 to 4000 mg display beneficial effects to both blood lipid profile parameters and antioxidant status [83–91] as also to total body mass index (BMI) and fat contents [92]. In these human trials, it was reported that curcumin supplementation decreased total cholesterol (TC), low density cholesterol (LDL-C), TC/HDL-C ratio, apolipoprotein B (Apo B), triglycerides (TG), non-high-density lipoprotein cholesterol (non-HDL-C), lipoprotein A (Lp(a)), serum Cu/Zn and even plasma fibrinogen (PF), serum lipid peroxides (SLP) and serum pro-oxidant–antioxidant balance (PAB). In the same studies, beneficial serum parameters, such as high-density cholesterol (HDL-C) and apolipoprotein A (Apo A) showed to be significantly increased. Interestingly, in one study, lower curcumin doses evidenced a better effect to various lipid parameters, while higher doses showed to be less efficient [83]. The data obtained in the mentioned study might be a confirmation of the results reported by Baum et al. [84], which found that curcumin administration at 4000 mg/day for 6-months only affected TG levels, but failed to change other metabolic parameters, such as TC, HDL-C and LDL-C.

Similar findings were observed by Mohammadi et al. [88], where in obese patients only TG levels changed after 1-month curcumin supplementation. The most recent data suggest that curcumin has better cardioprotective effects when applied in combination with phytosterols [86]. Another study, where curcumin showed to be more effective in combination, was the clinical trial performed by Amin et al. [93], where patients with metabolic syndrome received black paper alone, turmeric alone or their combination for 8 weeks. In this study, after 4 and 8-weeks period, BMI, body fat percent (BF%), waist-circumference (WC), hip-circumference (HC), blood pressure (BP), lipid profile (cholesterol, HDL-C, LDL-C and TG), fasting blood glucose (FBG) and c-reactive protein (CRP) levels were measured. When applied alone, turmeric improved BMI, WC and BF% after 4 weeks, while following 8 weeks administration, a significant reduction in LDL-C and CRP levels was observed in these patients. However, when applied in combination with black paper, but in lower doses (60% of individual herbs), after 8 weeks, a marked improvement in all metabolic syndrome parameters was stated: BF%, FBG, cholesterol, TG, LDL-C, CRP levels decreased and HDL-C level raised.

2.7. Curcumin and gastrointestinal diseases

Up to now, several clinical trials has been performed on patients suffering from inflammatory bowel disease, irritable bowel syndrome as well as in those with ulcers, *Helicobacter pylori* infections and even pancreatitis (Table 7). Human studies assessing the

Table 5
Clinical trials on effect of curcumin to respiratory system disorders.

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Length	Number of patients/Study design	Reference
Recurrent respiratory tract infections					
NI	Reduction in RRTIs; significant skewing of CD8+T lymphocytes maturation; increased CD14 $^{+}$ TLR2-expressing cells; diminished CD14+/TLR4+ and IL10 by CD14 $^{+}$ cells production	Oral supplementation: lactoferrin and curcumin 1000 mg (900 mg lactoferrin +100 mg curcumin), 3000 mg/day	4 weeks	10 children; randomized clinical trial	[82]

Legend: IL10, interleukin 10; NI, not investigated; RRTIS, Recurrent respiratory tract infections; TLR, toll like receptor.

Table 6
Clinical trials on effect of curcumin to cardiovascular system disorders.

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Lenght	Number of patients/Study design	Reference
No	Decrease serum lipid peroxides (by 33%), lowering TC by 12%, increase HDL-C (by 29%)	Capsules of curcumin (98% pure), 500 mg/day	7 days	10 healthy subjects	[90]
No	Decrease PF in the range 240–290 mg/dl	Tablets of hydroalcoholic extract of *C. longa* (10 mg curcumin/tablet), 20 mg/day	15 days	8 high plasma fibrinogen subjects	[91]
No	Decreases significantly LDL-C and apo B; increases HDL-C and apo A	Tablets of hydroalcoholic extract of *C. longa* (10 mg curcumin/tablet), 20 mg/day	30 days	12 men with high LDL values	[91]
_	Increase total cholesterol; TC, LDL-C and HDL-C remained unchanged	Either 4000 mg/day curcumin, 1000 mg/day curcumin, or placebo	6 months	36 healthy subjects; randomized, double-blind, placebo-controlled trial	[84]
No	Reduce TC and LDL-C levels; increase HDL-C levels	Escalating doses (low: 15 mg, 3 times/day; moderate: 30 mg, 3 times/day; high: 60 mg/3 times/day)	8 weeks	75 ACS patients; randomized double-blind controlled dose escalating trial	[83]
No	Decrease plasma TG levels, β-amyloid protein concentrations, plasma sICAM readings and plasma ALT activities; lower salivary amylase levels; increase salivary radical scavenging capacity, plasma CAT and myeloperoxidase activities, plasma nitric oxide	Optimized curcumin from *C. longa* root powder, 80 mg/day	4 weeks	38 patients, randomized double-blind placebo controlled parallel trial	[85]
_	Reduce serum TG, but not in other lipid profile parameters, as well as BMI and body fat	C3 Complex capsules (Sami Labs LTD, Bangalore, India) containing 500-mg curcuminoids plus 5 mg bioperine	30 days	30 obese patients; randomized, double-blind, placebo-controlled, crossover trial	[88]
_	Decrease serum PAB, but not in antibody titers of Hsp27 (anti-Hsp27) and oxLDL (anti-oxLDL)	Capsules containing 500 mg C3 Complex curcuminoids formula plus 5 mg bioperine	30 days[a]	30 obese patients, randomized, double blind, crossover trial	[88]
_	Increase HDL-C, reduced LDL-C, TG and TC/HDL-C ratio	Curcumin extract capsule (630 mg), 1890 mg/day	12 weeks	65 metabolic syndrome patients; randomized, double-blind, placebo-controlled trial	[89]
No	Reduce serum LDL-C, non-HDL-C, TC, TG and Lp(a); elevated HDL-C levels	Capsules containing 500 mg C3 Complex (95% curcuminoids) plus 5 mg bioperine, 1000 mg/day	8 weeks	100 patients, randomized double- blind placebo-controlled parallel trial	[134]
_	Significantly reduced pulse wave velocity, increase serum adiponectin and decrease leptin levels; reduce homeostasis model assessment-insulin resistance, TG, uric acid, visceral fat and total body fat	Capsules containing turmeric extract (calculated for 250 mg of curcuminoids), 1500 mg/day	9 months	240 type II diabetic patients; randomized, double-blinded and placebo-controlled clinical trial	[92]
No	Increase serum Zn/Cu and reduce Cu/Zn; no significant changes in serum Zn and Cu levels, nor in SOD activity	Capsules containing 500 mg C3 Complex (95% curcuminoids) plus 5 mg bioperine, 1000 mg/day	4 weeks	60 patients; randomized double-blind crossover trial	[87]
_	*4 weeks:* turmeric alone improved BMI, WC and BF%. Combination improved all parameters except HDL-cholesterol with lower FBG and LDL-C *8 weeks*: turmeric reduced LDL-C and CRP Combination group reduced BF%, FBG, TC, TG, LDL-C, CRP and raised HDL-C	Either black seeds (1.5 g/day), turmeric (2.4 g/day), or combination (900 mg black seeds and 1.5 g turmeric/day) or placebo	8 weeks	250 healthy males positive for metabolic syndrome; double-blinded, randomized, placebo-controlled trial	[93]
No	PS–CC resulted in a greater TC reduction (11.0%) and LDL-C (14.4%) than either of treatments alone; Plasma HDL-C and TG levels remained unchanged	Placebo (PL, no phytosterols or curcumin), phytosterols (PS, 2 g/d), curcumin (CC, 200 mg/d) or a combination of PS and curcumin (PS-CC, 2 g/d–200 mg/d, respectively)	4 weeks	70 hypercholesterolemic patients; double-blinded, randomized, placebo-controlled, 2 × 2 factorial trial	[86]

[a] Then crossed over to alternate treatment following a 2-week washout period. Legend: ACS, acute coronary syndrome; ALT, alanine aminotransferase; Apo A, apolipoprotein A; Apo B, apolipoprotein B; BF%, body-fat percent; BMI, body mass index; CAT, catalase; CRP, C-reactive protein; Cu, coper; FBG, fibrinogen; HDL-C, high-density lipoprotein cholesterol; Hsp27, heat shock protein 27; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; oxLDL, oxidized low-density lipoprotein; PAB, pro-oxidant-antioxidant balance; PF, plasma fibrinogen; sICAM-1, soluble intracellular adhesive molecule 1; SOD, superoxide dismutase; TC, total cholesterol; TG, triglycerides; WC, waist-circumference; Zn, zinc.

curcumin effects on pancreatitis are very scarce. The only study where patients with tropical pancreatitis were treated with curcumin, demonstrated that 500 mg curcumin combined with piperine led to a significant reduction of erythrocyte malondialdehyde (MDA) levels, a direct indicator of curcumin's antioxidant action [94]. On the other hand, neither pain evaluation scores nor glutathione (GSH) levels were different from placebo group.

The curcumin effects on gall bladder were investigated in two different studies enrolling healthy subjects, where 20–80 mg curcumin were given as a single dose; afterwards gall bladders were measured by an ultrasound technique. It has been found that up to 2 h after single curcumin dose administration, gall bladder dimensions reduced in a dose dependent manner [95,96]. In patients with biliary dyskinesia, a faster reduction in dumpy and colicky pain was stated in group receiving Cholagogum F, when compared with placebo group [97].

Table 7
Clinical trials on effect of curcumin to gastrointestinal system disorders.

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Lenght	Number of patients/Study design	Reference
Hepatoprotective effects					
No	AST, ALT and BR remained unchanged; weight gain and decreased ESR	Curcumin (25%) and hydroethanolic extract of *Tinospora cordifolia* (50%) containing 1000 mg each divided, 2 doses/day	4 months	528 patients on antitubercular therapy; randomized controlled clinical trial	[107]
NI	Reduce ALT, AST levels; no significant changes in blood GLU levels	Capsule 500 mg fermented turmeric powder standardized to 0.79 mg curcumin per 1.0 g powder; 3.0 g/day	12 weeks	60 subjects with elevated ALT levels and normal glucose levels; randomized, double-blind, placebo-controlled trial	[108]
Rare (3/40), stomachache and nausea	Reduced weight and BMI; decrease serum TC, LDL-C, TG, AST, ALT, FBG and HbA1c levels; improve liver ultrasonographic findings	Amorphous dispersion of curcumin formulation (500 mg/day equivalent to 70 mg curcumin)	8 weeks	80 ultrasonographic evidence of NAFLD patients; randomized double-blind placebo-controlled trial	[109]
Pancreatitis					
NI	Reduced erythrocyte MDA and increased GSH levels	Curcumin (500 mg) combined with piperine (5 mg)	6 weeks	20 tropical pancreatitis patients; randomized study	[94]
Gallbladder					
NI	Increase gall bladder contraction after 0.5, 1, 1.5 and 2 h curcumin administration	20 mg curcumin, single dose	1 day	12 healthy subjects; randomized, double blind, placebo controlled, crossover designed study	[95]
NI	Increase gall bladder contraction 2 h after curcumin administration, dose-dependent effect	20, 40 or 80 mg of curcumin, single dose	1 day	12 healthy subjects, randomized, single blind, III phase, crossover designed study	[96]
Biliary dyskinesia					
NI	Faster dumpy reduction and colicky pain in treatment group	Cholagogum F Nattermann (dried extracts from Schöllkraut and Curcuma)	3 weeks	39 patients, placebo-controlled double-blind study	[97]
Irritable bowel syndrome					
NI	Improve IBSQOL scale results in both groups	72 mg of turmeric extract (Cynara Turmeric, Lichtwer Pharma UK), 72 mg/day or 144 mg/day	8 weeks	207 healthy adults; partially blinded, randomized, two dose, pilot study	[101]
NI	Increase bowel motility; hydrogen producing flora activation in colon	Curry mixture containing 0.5 g turmeric, 0.5 g cayenne paper, 3 g coriander seeds, 0.5 g cumin seeds (Gaban, Tokio, Japan). Curcumin content corresponded to 5.48 mg curcumin +1.62 mg demetoxycurcumin +1.15 mg bismetoxycurcumin/meal	1 day	8 healthy adults; randomized crossover study	[102]
Inflammatory bowel disease					
No	Decrease in inflammatory CRP and ESR indices in ulcerative proctitis patients; decrease CDAI, ESR and CRP indices in Crohn disease patients	Ulcerative colitis patients recieved 1100 mg/day for 1 month and 1650 mg/day for one additional month; Crohn disease patients received 1080 mg/day for 1 month and 1440 mg/day for additional two months	2–3 months	10 ulcerative proctitis and Crohn disease patients, open label pilot study	[100]
No	Reduce recurrence rate in curcumin group	1–3 g/day of curcumin combined with sulfasalazine or mesalamine	6 months	89 ulcerative colitis patients, randomized, multicenter, double blind, placebo-controlled trial	[98]
No	53.8% receiving curcumin achieved clinical remission at week 4 vs 0% in placebo group; clinical response was achieved by 65.3% in the curcumin group vs 12.5% in placebo group; endoscopic remission observed (38%) in curcumin group vs none in placebo group	Curcumin capsules (3000 mg/day) or an identical placebo with continued mesalamine	1 month	50 mesalamine-treated patients with mild-to-moderate active UC; multicenter randomized, double-blind, placebo-controlled trial	[99]
Peptic ulcer					
NI	Ulcers disappeared after 4 (12 patients), 8 (18 patients) and 12 weeks (19 patients) treatment; decrease in abdominal pain and discomfort	Capsule-filled turmeric was given orally in the dose of 2 capsules (300 mg each) five times daily, 3000 mg/day	12 weeks	45 patients, 25 with peptic ulcer and 20 with erosions, gastritis and dyspepsia; Phase II clinical trial	[106]
NI	Ulcers reduction	Capsules of turmeric (250 mg), 1000 mg/day or liquid antacid (30 ml), 1200 ml/day	6–12 weeks	60 ulcer patients, randomized controlled trial	[105]
Helicobacter pylori infection					
NI	12% treated of *H. pylori* infection; decrease in overall	Curcumin (30 mg) combined with lactoferrin (100 mg), N-acetylcysteine	1 week	25 *H. pylori* positive patients with functional dyspepsia	[103]

(*continued on next page*)

Table 7 (*continued*)

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Lenght	Number of patients/Study design	Reference
	symptoms severity and reduction of serologic signs of gastric inflammation	(600 mg), and pantoprazole (20 mg), twice/day			
NI	*H. pylori* eradication rate in patients that received OAM treatment was significantly higher than that receiving curcumin (78.9% vs 5.9%); limited effect on inflammatory cytokines production	Either one-week course of omeprazole-based triple regimen (20 mg omeprazole, 1000 mg amoxicillin, and 800 mg metronidazole) each given orally twice/day; or a four-week course of turmeric tablet (2100 mg/day)	1week OAM/4 weeks curcumin	*H. pylori*-infected gastritis patients	[104]

Legend: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BR, bilirubin; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBG, fibrinogen; GLU, glucose; GSH, glutathione; HbA1c, glycated hemoglobin; IBSQOL, irritabile bowel symptoms quality of life scale; LDL-C, low-density lipoprotein cholesterol; MDA, malonylaldehyde; NAFLD, non-alcoholic fatty liver disease; NI, not investigated; OAM, omeprazole-amoxicillin-metronidazole; TC, total cholesterol; TG, triglycerides.

Regarding inflammatory bowel disease, several studies has been done on patients with Crohn disease, ulcerative colitis and ulcerative proctitis [98–100]. Holt et al. [100] studied the effect of orally administered curcumin in two rising doses on patients with ulcerative proctitis and Crohn disease. It has been reported that ulcerative proctitis patients which consumed curcumin for 2 months had decreased inflammatory markers, namely CRP and erythrocyte sedimentation rate (ESR). On the other hand, patients with Crohn disease showed reduction of Crohn's Disease Activity Index (CDAI), CRP and ESR. The study performed on patients with ulcerative colitis showed that after oral curcumin administration (1–3 g) in combination with sulfasalazine or mesalamine for 6 months, led to a significant reduction of recurrence rate [98] in treated patients. Finally, a recent study performed by Lang et al. [99] demonstrated that patients with ulcerative colitis, which received curcumin (3 g dose) for 1 month, had very good results when compared to the placebo group. Indeed, in curcumin group, 53.8% achieved clinical remission at week 4 vs 0% in placebo group, while clinical response was achieved by 65.3% in curcumin group vs 12.5% in placebo group.

Also, endoscopic remission was observed in 38% of curcumin group patients, in contrast to none of the placebo group patients. Clinical trials have also demonstrated that, in healthy participants who consumed turmeric extract, irritable bowel syndrome symptoms were markedly improved [101], in the same way of bowel motility and intestinal microbial flora after consumption of a meal containing curry mixture [102].

On the other hand, curcumin has been reported to be efficient against *H. pylori* infection, where an oral administration of 30 mg curcumin in combination with lactoferrin (100 mg), N-acetylcysteine (600 mg) and pantoprazole (20 mg) for only 1-week led to reduction of the overall symptom severity, inflammation and, in 12% of cases a complete recovery was observed [103]. Still, curcumin alone, applied for 4 weeks at 2100 mg/day caused very low eradication rate and had limited effect on inflammatory cytokines production [104]. In addition, curcumin showed to be effective in the treatment of gastric ulcers, erosions and dyspepsia [105,106], where it has been reported that after curcumin (1–3 g/day) administration up to 12 weeks, ulcers and erosions were reduced or even eradicated, while abdominal pain and discomfort markedly decreased.

2.8. Curcumin and liver diseases

The first study assessing the hepatoprotective effects of curcumin was carried out in patients with tuberculosis, focusing on their ability to prevent anti-tuberculosis treatment (ATT)-induced hepatotoxicity (Table 7). Although to be observed an increase in liver aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin concentrations in the control group, in the intervention group these values remained unchanged. In addition, a significant weight gain and a decrease in erythrocyte sedimentation rate were stated in the intervention group [107]. The hepatoprotective effects of curcumin were also confirmed afterwards, in the study carried out by Kim et al. [108], where fermented turmeric powder was administered in subjects with elevated ALT levels. Together with ALT, AST, gamma-glutamyl transferase (GGT), total bilirubin (TB) levels, and lipid profiles were measured as well. Group treated with fermented turmeric powder showed significant reduction in ALT levels after 12 weeks treatment, together with AST levels. Considering other parameters, GGT levels showed a tendency to decrease, while serum alkaline phosphatase (ALP), TB, and lipid profiles levels remained relatively unchanged. In patients with non-alcoholic fatty liver disease (NAFLD), a chronic liver condition characterized by neutral lipids accumulation in liver cells, curcumin also displayed a promising potential. The study of Rahmani et al. [109] reported an improvement in lipid profile status and a significant reduction in AST and ALT levels, as also of body weight and BMI, at same time that improved liver ultrasonographic findings in patients with NAFLD receiving curcumin supplementation.

2.9. Curcumin and genitourinary tract diseases

Curcumin has also shown an interesting ability to improve symptoms of various genitourinary conditions. Only a small number of clinical trials investigated the curcumin role in the treatment of kidney diseases (Table 8). In 2005, Shoskes et al. [110] demonstrated beneficial effects of curcumin supplementation on early graft function in dialysis-dependent patients after renal transplantation. It was found that curcumin enhanced early graft function (EGF), lowered serum creatinine (SC) and reduced tremor and acute rejection incidence. Also, delayed graft function (DGF) was not observed at high dose curcumin-treated groups. In lupus nephritis patients, curcumin significantly reduced proteinuria in comparison to control group [111], as also in those suffering from diabetic nephropathy [112]. Jimenez-Osorio et al. [113] found that curcumin was able to attenuate lipid peroxidation in individuals with nondiabetic proteinuric chronic kidney disease (NDP-CKD) and to enhance the antioxidant capacity in subjects with diabetic proteinuric chronic kidney disease (DP-CKD), despite failed in improving proteinuria, estimated glomerular filtration rate, or lipid profile.

In chronic prostatitis patients, the oral administration of prulifloxacin combined with *Serenoa repens*, *Urtica dioica*, quercetin and

Table 8
Clinical trials on effect of curcumin to urogenital system disorders.

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Lenght	Number of patients/Study design	Reference
Renal transplantation					
NI	DGF not recorded; EF incidence increased; SC lowered; incidence of acute rejection and tremor reduced	Curcumin (480 mg) and quercetin (20 mg)	1 month	43 dialysis dependent cadaveric kidney recipients, randomized placebo-controlled trial	[110]
Diabetic nephropathy					
No	Decreased serum TGF-β, IL-8 levels and proteinuria	Capsule containing 500 mg turmeric, of which 22.1 mg was active ingredient curcumin (3 capsules daily)	8 weeks	40 overt type II diabetic nephropathy patients, randomized, double-blind and placebo-controlled study	[112]
Lupus nephritis					
NI	Decrease in proteinuria and hematuria; lowered blood pressure	Capsule (500 mg turmeric corresponding to 22.1 mg curcumin), 3 capsules daily	12 weeks	24 lupus nephritis patients; randomized and placebo-controlled study	[111]
Chronic kidney disease					
NI	Reduce in lipid peroxidation in NDP-CKD patients; increase antioxidant capacity in DP-CKD patients	Curcumin capsules (320 mg/day) or placebo	8 weeks	101 nondiabetic or diabetic proteinuric CKD patients; randomized double-blind placebo-controlled clinical trial	[113]
Chronic bacterial prostatitis, type II					
NI	100% patients with no symptoms associated with CBP after 6-month therapy	Antibiotic therapy associated with *Serenoa repens* (160 mg), *Urtica dioica* (120 mg) (ProstaMEV®), quercitin (100 mg) and curcumin (200 mg) tablet (FlogMEV®)	6 months	143 patients; randomized, long-term follow-up study, type II	[114]
Chronic prostatitis/Chronic pelvic pain syndrome, type III					
NI	Improvement of NIH–CPSI, IIEF-5, PEDT, peak flow and VAS	Rectal suppositories of curcumin extract 350 mg (95%) and calendula extract 80 mg (1 suppository/day)	1 month	60 patients; phase II, randomized, single-blinded, placebo-controlled clinical trial	[115]

Legend: CBP, chronic bacterial prostatitis; CKD, chronic kidney disease; DGF, delayed graft function; DP-CKD, diabetic proteinuric chronic kidney disease; EF, early graft function; IIEF-5, International Index of Erectile Function; IL-8, interleukin 8; NDP-CKD, non-diabetic proteinuric chronic kidney disease; NI, not investigated; NIH–CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PEDT, Premature Ejaculation Diagnostic Tool; SC, serum creatinine; TGF-β, tumor growth factor; VAS, visual analog scale.

curcumin tablet extracts had positive effect on QoL scores of treated patients. In addition, after 6-months treatment, none of the patients experienced disease recurrence, which was not the case of the group treated with antibiotics alone [114]. Another study on chronic prostatitis/chronic pelvic pain syndrome type III patients, showed very promising results, when combining curcumin and calendula extracts, and administered as rectal suppositories. The authors found a marked improvement on patients' symptom scores, measured as a reduction of total National Institutes of Health Chronic Prostatitis Symptom Index (NIH–CPSI). Suppositories also displayed a high efficacy in terms of pain relief, voiding symptoms and urinary flow, after 1-month treatment when compared to placebo group [115].

2.10. Curcumin and metabolic disorders

2.10.1. Curcumin and diabetes

It is well known that T2DM represents a condition where body is not able to properly respond to insulin produced. This condition is highly related with inflammatory cytokines production and oxidative stress; so, due to anti-inflammatory and antioxidative action of curcumin, it might be an effective therapeutic agent. The option of using curcumin in the treatment of this condition was firstly investigated by Srinivasan [116], who found that 5 g of turmeric powder was able to decrease blood sugar in one patient diagnosed with T2DM. More recent and numerous studies have confirmed these findings (Table 9). Wickenberg et al. [117] carried out an interesting trial to investigate *C. longa* effects on post-prandial plasma glucose, insulin levels and glycemic index (GI) in healthy subjects. After a single dose (6 g) of turmeric taken together with oral glucose tolerance test (OGTT), no changes were observed on both glucose levels nor GI, but significant changes were recorded on insulin levels, suggesting that turmeric affect insulin secretion. In prediabetic patients, an intake of 1500 mg/day curcumin lead to an improvement of β-cells' overall function, and, even more important, none of curcumin-treated group has been diagnosed with T2DM [92]. In another study, curcuminoids supplementation significantly decreased fasting blood glucose (FBG), hemoglobin A1c test (HbA1c) and insulin resistance index (HOMA-IR), total serum free fatty acids (FFAs) and TG, while increased lipoprotein lipase (LPL) activity in T2DM patients [118]. Very similar results were found in the study performed by Selvi et al. [119], where decreased FBG, together with improved antioxidant status and inflammatory markers were recorded in patients receiving oral curcumin combined with standard metformin therapy. On the other hand, Rahimi et al. [120] found that nanocurcumin administration for 3 months decreased HbA1c, FBG and lipid profile in T2DM patients. Also, the authors found that curcumin represents a very useful supplement during glyburide therapy of T2DM, due to its permeability glycoprotein (P-gp) inhibitory activity, resulting in an increase of glyburide bioavailability [121]. Since patients in this study exhibited improvement in blood glucose and lipid profile levels after curcumin 10 day-treatment, it is clear that this compound can be very useful to diabetic patients on glyburide therapy.

2.10.2. Curcumin and obesity

Promising results where curcumin improved lipid status as also fat content on treated individuals set the base for studies on obese

Table 9
Clinical trials on effect of curcumin to metabolic disorders.

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Lenght	Number of patients/Study design	Reference
Type II diabetes					
No	Reduce blood sugar levels	Turmeric powder	3 months	1 T2DM patient	[116]
NI	No significant effect on glucose response; raise in insulin AUCs 30 min and 60 min after OGTT including *C. longa*	75 g OGTT was administered together with capsules containing placebo or *C. longa* (6000 mg)	Single dose	14 healthy subjects; crossover trial	[117]
No	Better overall β-cells function, higher HOMA-β and adiponectin; lower C-peptide and HOMA-IR levels; none diagnosed with T2DM	Capsules (250 mg of curcuminoids), 1500 mg/day	9 months	240 prediabetic patients, randomized, double-blinded, placebo-controlled trial	[92]
NI	Decrease in FBG, HOMA-IR, serum total FFAs, TG; increase LPL activity	Turmeric rhizome extract (curcumin 36.06%; demethoxycurcumin, 18.85%; bisdemethoxycurcumin, 42.58%), 300 mg/day	12 weeks	100 overweight/obese T2DM patients; double-blind, placebo-controlled trial	[118]
NI	higher glyburide levels, unchange C_{max} of glyburide; decrease glucose, LDL, VLDL and TG levels; increase HDL	Capsule (475 mg curcumin), Zenith Pharmaceuticals, Bangalore, India, combined with 5 mg Daonil, once/day	11 days	8 T2DM patients on glyburide therapy, open-label, randomized control trial	[121]
NI	Decrease FBG, HbA1c, lipid peroxidation and MDA levels, and enhance total antioxidant status; reduce LDL-C, non-HDL-C; and inflammatory marker hsCRP	Standard metformin therapy with turmeric powder (2 g/day, 4 capsules, 500 mg each)	4 weeks	60 diabetic patients on metformin therapy; open label randomized clinical trial	[119]
–	Decrease in HbA1C, FBG, TG and BMI	Nano-curcumin (as nanomicelle 80 mg/day)	3 months	70 T2DM; double blind randomized placebo control add-on clinical trial	[120]
Obesity					
NI	Reduce serum TG, but not in other lipid profile parameters nor in BMI and body fat	C3 Complex capsules (Sami Labs LTD, India) containing 500 mg curcuminoids plus 5 mg bioperine	30 days	30 obese individuals, randomized, double-blind, placebo-controlled, crossover trial	[88]
NI	No significant changes in none of investigated parameters (oxidative stress or inflammation, global metabolic parameters)	Supplementation with red piper (1000 mg/day) or turmeric (2800 mg/day)	10-week	62 overweight/obese females with systemic inflammation; randomized, doubled-blinded, placebo-controlled, crossover design	[122]
NI	Reduce serum IL1β, IL-4 and VEGF levels; IL-2, IL-6, IL-8, IL-10, IFNγ, EGF, and MCP-1 were unchanged	C3 Complex formula, 1000 mg/day	4 weeks	30 obese individuals, randomized, double blind, crossover trial	[124]
No	Increase weight loss (from 1.88 to 4.91%), enhance body fat reduction percentage (from 0.70 to 8.43%), and BMI reduction (from 2.10 to 6.43%), increase waistline reduction (from 2.36 to 4.14%), improve hip circumference reduction (from 0.74 to 2.51%)	Curcumin complexed with phosphatidylserine in phytosome form	30 days	44 obese subjects; randomized, controlled trial	[123]
β-thalassemia					
NI	Decrease MHb and H_2O_2-induced MDA; no changes in Hb levels; decrease SOD and GSH-Px activities in RBC; increase reduced GSH levels	Capsules (500 mg/day), curcumin, demethoxycurcumin, and bisdemethoxycurcumin in 1:0.3:0.1 ratio	12 months	21 β-thalassemia/Hb E patients	[125]
NI	Decrease iron load, oxidative stress, and coagulation potential and increase antioxidant capacity and hemoglobin concentration	Curcumin 500 mg/day, 200 mg/day of N-acetylcysteine, and 50 mg/kg/day deferiprone	12 months	60 β-thalassemia/Hb E patients;	[126]
NI	Decrease MDA, total and direct bilirubin levels; increase total antioxidant capacity; Hb, serum iron, ferritin, catalase, and vitamin E levels were not changed	Capsules (1000 mg/day) (Aburaihan Pharmaceutical Company, Tehran, Iran)	12 weeks	68 patients, A Double-Blind Randomized Controlled Clinical Trial	[127]
NI	Reduce serum levels of NTBI, ALT and AST; no significant changes in hepcidin	500 mg curcumin capsules (1000 mg/day) or placebo	12 weeks	68 patients, double-blind randomized controlled clinical trial	[128]
Acquired immunodeficiency syndrome (AIDS)					
NI	No viral load reduction; no CD4 cells counts increase	Low (1500 mg/day) or high (2500 mg/day) doses	8 weeks	40 AIDS patients; randomized	[129]

Legend: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; EGF, epidermal growth factor; FBG, fasting blood glucose; FFAs, total serum free fatty acids; GSH, glutathione; GSH-Px, glutathione peroxidase; H_2O_2, hydrogen peroxide; Hb, hemoglobin; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, insulin resistance index; IFNγ, interferon gamma; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MHb, methemoglobin; NI, not investigated; NTBI, non-transferrin bound iron; OGTT, oral glucose tolerance test; RBC, red blood cells; SOD, superoxide dismutase; T2DM, type II diabetes mellitus; TG, triglycerides; VEGF, vascular endothelial growth factor; VLDL, very-low-density lipoprotein cholesterol.

patients. Only several clinical trials reported results on curcumin obesity effects (Table 9). The first one investigated the effect of curcumin oral supplementation on lipid profile parameters, BMI and glucose levels in obese individuals. The results demonstrated significant changes only in TG levels, while other parameters remained unchanged after 30 days-curcumin administration [88]. The results obtained by Nieman et al. [122] demonstrated that 4-week supplementation with turmeric in dose of 2.8 g/day does not alter oxidative stress or inflammatory parameters in systemic inflammation overweight/obese females, nor cause a significant shift in global metabolic profile. Although the mentioned studies showed no encouraging results, recent findings showed positive effects of curcumin on body weight and BMI. After one month of 1.6 g/day curcumin oral administration (in the form of phytosome in combination with 8 mg piperine), significant improvements in BMI, body fat and body measures were reported [123]. BMI and body weight reduction were also recorded in the study of Rahmani et al. [109], who investigated these parameters in NAFLD patients. Together with the described results, it was also reported that oral curcumin administration can modulate immune response in obese individuals, via altering the circulating concentrations of IL-1β, IL-4, and VEGF [124].

2.10.3. Curcumin and β-thalessemia

Thalassemia is a common hereditary disorder, leading to the imbalance ratio between 2 types of paired globin's that make up hemoglobin. In this condition, heme group is separated from globin and free radicals are generated following peripheral hemolysis, premature apoptosis and anemia [125]. In the light of curcumin's antioxidant potential, it could be used for oxidative stress amelioration in these patients (Table 9). The study of Kalpravidh et al. [125] investigated the oral curcumin effect on oxidative status of β-thalessemia/HbE patients. After 12 months of application, curcumin did not have any effect on hematological parameters, as also on liver and kidney function tests and lipid profiles. However, curcumin decreased methemoglobin (MHb), superoxide dismutase (SOD), red blood cells MDA, glutathione peroxidase (GSH-Px), serum ferritin and serum non-transferrin bound iron (NTBI), while increased glutathione (GSH) levels, all implying an oxidative stress reduction in these patients. In the same type of patients (β-thalassemia/HbE), an antioxidant cocktail containing curcumin, N-acetylcysteine and deferiprone improved anemia, oxidative stress, iron overload and hypercoagulable state, as reported by Yanpanitch et al. [126]. Another study, but on β-thalassemia major patients, a pronounced decrease in serum MDA levels, total and direct bilirubin and an increase of total antioxidant capacity after 12-weeks curcumin oral intake were stated [127]. Together with this, recent investigation of curcumin's effect on iron overload, hepcidin level and liver function in β-thalassemia major patients demonstrated that this compound was able to alleviate iron burden and liver dysfunction, by reducing NTBI, ALT, and AST levels in patients receiving 12-week curcumin supplementation [128].

2.10.4. Curcumin and acquired immunodeficiency syndrome (AIDS)

There was only one study on AIDS patients, where the curcumin administration at high and low doses were investigated for antiviral effectiveness. It was found that curcumin does not affect viral load nor CD4 counts [129] (Table 9).

2.11. Toxin neutralizing effects of curcumin

Antioxidative properties of curcumin prompted studies on its efficacy against genotoxicity after arsenic exposure [130,131]. Volunteers exposed to groundwater arsenic and receiving 1000 mg curcumin/day showed reduced DNA damage in lymphocytes, as well as a decrease in ROS and lipid peroxidation levels [130]. Arsenic-induced oxidative stress prevention and repairing enzymes induction triggered by curcumin in arsenic-exposed population of West Bengal has been investigated by Roy et al. [131]. In their study, results indicated that curcumin suppressed 8-hydroxy-20-deoxyguanosine level and OGG1 (the essential protein involved in oxidative stress-induced DNA demethylation) expression, while increased DNA repairing enzymes expression (Table 10).

The study of Sasaki et al. [131] investigated both blood-ethanol and blood-acetaldehyde levels, 30, 60, 120 and 180 min after ethanol consumption with 30 g curcumin (Theracurmin). The results showed lower plasma acetaldehyde concentrations in subjects who drank curcumin in comparison to those who drank only mineral water. In the case of ethanol, both groups showed similar results. Thus, in light of these facts, curcumin has a prominent potential in reducing alcohol intoxication.

2.12. Curcumin and cancer treatment

Many clinical trials have been carried out to evaluate the beneficial effects of curcumin in cancer patients. It has been confirmed that it can provide symptomatic relief, as well as improve tumor markers and other parameters of various cancer conditions, including skin lesions, multiple myeloma, head, neck and orbital tumors, brain, lung, breast, prostate, colon, colorectal and prostate cancers. The curcumin therapeutic potential in distinct cancers treatment, reported in clinical studies enrolling human patients, is presented and discussed in Table 11. In patients with cancerous and precancerous skin lesions, oral submucosal

Table 10
Clinical trials on effect of curcumin to intoxications.

Adverse effects, toxicity	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Lenght	Number of patients/Study design	Reference
Chronic arsenic exposure					
NI	Reduce DNA damage; retard ROS generation and lipid peroxidation; raise levels of antioxidant activity	Curcumin capsules blended with piperine (20:1), 1000 mg/day	3 months	286 groundwater arsenic-exposed volunteers; a field study	[130]
No	Arsenic-inhibited DNA repair was induced by curcumin, both at protein and genetic levels	Curcumin capsules (500 mg), each capsule containing curcumin along with piperine (obtained from black pepper) at 100: 1 ratio, twice/day	3 months	66 volunteers	[131]
Alcohol intoxication					
–	Reduced acetaldehyde levels in blood	100 ml mineral water containing Theracurmin 30 mg, or mineral water only following the ingestion of 0.5 ml/kg ethanol	Single dose	7 healthy males	[131]

Legend: DNA, deoxyribonucleic acid; NI, not investigated; ROS, reactive oxygen species.

Table 11
Clinical trials on efficacy of curcumin to different malignant diseases.

Adverse effects, toxicity	Overall effect	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Lenght	Number of patients/ Study design	Reference
Skin lesions						
1/62	+	Symptomatic relief including reduction of smell (90%), itching (100%), dry lesions (70%), lesion size and pain (10%)	Ointment containing turmeric ethanolic extract	–	62 external cancerous lesions patients	[135]
NI	+	Decreased micronuclei number in lymphocytes and oral mucosal cells in OSF patients treated with all three turmeric forms	Capsules containing turmeric oil (600 mg oil/day mixed with 3 g extract), turmeric oleoresin (600 mg/day mixed in 3 g extract in three doses) and turmeric alcoholic extract (3 g/day in three doses); orally administered	3 months	58 oral submucosal fibrosis patients; phase I trial	[136]
No	+	Improved histological status of precancerous lesions at all applied doses	0.5–8.0 g/day; oral administration	3 months	25 various precancerous lesions patients, phase I trial, dose escalation study	[137]
NI	n.o.	No significant changes in VAS, NRS, erythema, ulceration and total clinical scores between placebo and curcuminoid groups	Capsules of curcuminoids (turmeric standardized extract, curcumin C3 complex) 2 g/day in 2 divided doses for 7 weeks, 7 days 60 mg prednisone/day	7 weeks	100 patients, phase II trial, randomized, double blind, placebo-controlled trial	[138]
NI	+	Improved pain scores and lesions size, increased serum and salivary vitamin C and E levels; decreased MDA and 8-OHdG levels in all three groups	1 g curcumin tablet, 900 mg curcumin +80 mg desmethoxycurcumin +20 mg bisdesmothoxycurcumin	1 week	25 oral leucoplakia, 25 oral submucous fibrosis, 25 lichen planus patients, and 25 healthy individuals	[139]
Myeloma						
NI	+	Decreased paraprotein and urinary N-telopeptide of type I collagen in curcumin treated group	Capsule containing curcumin C3 complex (1000 mg curcuminoids = 900 mg curcumin +80 mg desmetoxycurcumin +20 mg bisdesmothoxycurcumin); oral administration, 2 tablets twice daily (4 g/day)	12 months	26 monoclonal gammopathy patients of undetermined significance; single blind, crossover pilot study	[140]
No	+	Downregulation of NF-κB, STAT3 and COX-2 expression	Curcumin alone 2,4,6,8 and 12 g/day or combined with bioperine (10 mg/day)	12 weeks	29 multiple myeloma patients; phase I/II study	[141]
Orbital pseudotumors						
No	+	Full recovery in 4 patients; swelling regression, but limited movement in 1 patient	Capsules (375 mg of curcumin), 1125 mg/day	6–22 months	8 idiopathic inflammatory orbital pseudotumors patients	[142]
Head and neck squamous cell carcinoma						
No	+	Reduction of IKKβ kinase activity; reduced expression of salivary cytokines	Two curcumin tablets (Yarrow Formulas Curcumin 95), 1 g, chewing for 5 min	5 min	39 head and neck squamous cell carcinoma patients; pilot study	[143]
Breast cancer						
Maximal tolerated dose: 8 g/day	+	CEA tumor marker decrease; CA15.3 tumor markers remained content; decreased VEGF marker pointing to antiangiogenic effect	500 mg capsules (450 mg curcumin), 0.5–8.0 g/day, in combination with intravenous Docetaxel therapy (100 mg/m^2)	6 cycles-treatment, 7 consecutive days per cycle	14 metastatic breast cancer patients; open-label, Phase I trial	[144]
Lung cancer						
No	+	Reduced mutagens secreted in urine after turmeric treatment; no changes in serum AST, ALT, blood glucose, creatinine or lipid profile	Tablets (750 mg turmeric), oral administration of 1.5 g/day	30 days	22 patients (16 smokers and 6 non-smokers)	[145]
Prostate cancer						
NI	+	Significant decrease in PSA levels in group receiving supplement	Supplement containing combination of 40 mg soy isoflavones and 100 mg curcumin	6 months	85 patients with increased PSA levels; randomized, double blind trial	[146]
Pancreatic cancer						
No	+	Poor oral bioavailability; 1 patient showed stable disease for more than 18 months; 1 patient showed tumor regression accompanied by increased serum cytokines (IL6, IL8, IL10 and IL1); reduced expression of NF-κB, COX-2 and pSTAT3 in mononuclear blood cells	Capsule (900 mg curcumin, 80 mg desmethoxycurcumin, 20 mg bisdesmothoxycurcumin); 8 g/day	8 weeks	25 advanced pancreatic cancer patients; phase II trial, non-randomized	[147]
Yes (in 6 patients), abdominal fulness or pain	n.o.	Limited reduction (3 patients) in CA 19–9 tumor marker levels	Capsule (450 mg curcumin, 40 mg desmethoxycurcumin, 20 mg bisdesmothoxycurcumin), 8 g/day combined with intravenous administration of gemcitabine (1 g/m^2)	4 weeks	17 advanced pancreatic cancer patients; phase II trial	[148]

Table 11 (*continued*)

Adverse effects, toxicity	Overall effect	Effect of curcumin treatment	Treatment, dose and formulation of curcumin	Trial Lenght	Number of patients/ Study design	Reference
No	+	MST of 5.4 months; 1-year survival rate of 19%	Microbead form (C3 complex: curcumin 73% + desmethoxycurcumin 22% + bisdesmothoxycurcumin 4%), 8 g/dose, oral administration, 8 g/day combined with administration of gemcitabine (1 g/m2) and S-1	12 months	21 pancreatic cancer gemcitabine-resistant patients; phase I/II	[149]
Yes (in 2 patients), abdominal pain	+	Higher curcumin bioavailability; improved fatigue- and functioning-associated QoL scores	Theracurmin doses comprised 200 mg/body/day and 400 mg/body/day; daily oral dose was added to standard gemcitabine-based chemotherapy	–	16 pancreatic or biliary tract cancer patients who failed chemotherapy; phase I	[150]
Colorectal cancer						
No	+	Decreased lymphocytic GST activity (59%) at dose of 440 mg/day; leucocytic M1-G levels were unaffected by any treatment; detectable levels of curcumin and its metabolites in feces	Capsule (18 mg curcumin +2 mg desmetoxycurcumin) suspended in 200 mg essential oil derived from *Curcuma spp.*; oral administration 440 −2200 mg/day (corresponding to 36 −180 mg of curcumin)	29 days	15 advanced colorectal cancer patients; phase I trial, dose-escalation pilot study	[151]
No	+	Decreased inducible PGE_2 by 62% (day 1) and 57% (day 29); detectable levels of curcumin and its metabolites in plasma and urine	Capsule curcumin C3 complex (40 mg desmetoxycurcumin+10 mg bisdesmothoxycurcumin); oral administration 450–3600 mg curcumin/day	up to 4 months	15 advanced colorectal cancer patients; phase I dose-escalation study	[152]
No	+	Decreased M1-G level; COX-2 levels were not affected; detected metabolites of curcumin in healthy and malignant colorectal tissue samples and trace levels in peripheral blood	Turmeric extract (curcumin C3 complex) formulated in capsule; given orally in 3 doses: 3.6; 1.8 and 0.45 g/day	7 days (before surgery)	12 colorectal cancer patients, phase I trial	[153]
No	+	Decreased polyps' number (by 60.4%) and size (by 50.9%) after 6 month-therapy	Tablets Oxy-CU containing curcumin (480 mg) and quercetin (20 mg) administered orally 3 times/day	3–9 months	5 familial adenomatous polyposis patients, prior colectomy	[154]
NI	+	Increased body weight, tumor apoptotic cells number and p53 and Bax expression; reduced serum TNF-α levels, inhibited Bls-2 expression	Capsules containing 360 mg curcumin, orally administered 3 times/day	10–30 days	126 patients, randomized study	[155]
No	+	ACF were significantly reduced by higher curcumin dose	Capsule in 2 doses: 2 and 4 g/day, oral administration	30 days	44 patients (smokers), non-randomized, open labeled trial, phase IIa	[156]

Legend: 8-OHdG, 8-hydroxydeoxyguanosine; ACF, aberrant crypt foci; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CA 15.3, cancer antigen 15–3; CEA, carcinoembryonic antigen; COX-2, cyclooxygenase-2; GST, glutathione *S*-transferase; IL, interleukin; M1-G, DNA adduct formed by malondialdehyde; MDA, malonaldehyde; MST, median survival time; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NI, not investigated; PGE2, Prostaglandin E_2; PSA, prostate-specific antigen; pSTAT3, phosphorylated signal transducer and activator of transcription 3; QoL, quality of life; TNF-α, tumor necrosis factor alpha; VAS, visual analog scale.

fibrosis and oral leucoplakia, curcumin was applied in the form of capsules or an ointment [134–138]. In most of the trials, application of turmeric oil or extract caused symptomatic relief and improved the status of histological lesions. When applied in patients with myeloma, oral curcumin administration (1–12 g/day) led to a reduction in paraprotein and urinary N-telopeptide of type I collagen levels and downregulated NF-kB, STAT3 and COX-2 expression [139,140]. Furthermore, in patients with orbital pseudotumors, head and neck squamous carcinoma, breast, lung and prostate cancers, curcumin application also demonstrated beneficial effects, where reductions in tumors length and tumor markers, as well as a decrease in secreted mutagens were recorded [141–145]. However, although curcumin improved quality of life and tumor markers, as well as the serum cytokines and NF-kB, COX-2 and pSTAT3 expression, it evidenced a limited effect in patients with pancreatic cancer, which might be related to the fact that these patients are at an advanced stage of the disease [146–149]. Finally, in patients with colorectal cancer, curcumin intake, mainly in the form of C3 complex, led to a marked decrease in M1-G and serum TNF-α levels, polyps' number and size, and aberrant crypt foci, and to an increase in tumor apoptotic cells number, p53, Bax and Bls-2 expression [150–155].

3. Conclusions and future perspectives

The overall clinical highlighted data documented the promising potential of turmeric and its major constituent curcumin on different health conditions. From its large efficacy on oxidative-stress related disorders to its remarkable effect on malignant diseases, there is of utmost interest to still continue deepening knowledge on this promising matrix. Concerning to its incipient, but hopeful effect on distinct respiratory system disorders, besides to already underlined therapeutic ability to solve recurrent respiratory tract infections, further studies should be evolved to pioneer its efficacy in many other respiratory system-related conditions. Not least important to exploit, would be the curcumin effect on many other malignant disorders, given its epidemic incidence among worldwide population. Finally, a special emphasis should also be given to its noteworthy potential on both toxic and pollutants-exposure, since auto-immune-related disorders has been increasingly related to their cumulative exposure.

Author contributions

All authors (B.S., Z.S.-R., J.M., M.S.-R., N.V.A.K., N.M., and J.S.-R.) contributed equally to this work. Z.S.-R., M.S.-R., N.M., and J.S.-R. critically reviewed the manuscript. All the authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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