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Review

Curcumin Formulations for Better Bioavailability: What We Learned from Clinical Trials Thus Far?

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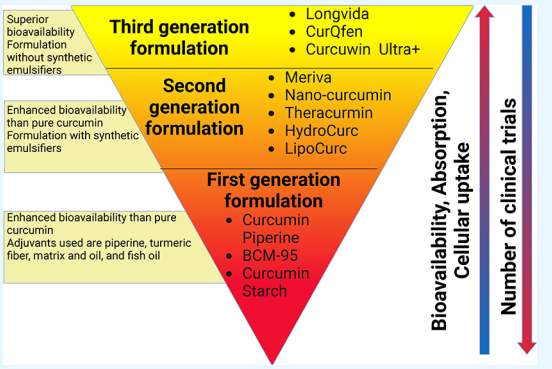
ABSTRACT: Curcumin has been credited with a wide spectrum of pharmacological properties for the prevention and treatment of several chronic diseases such as arthritis, autoimmune diseases, cancer, cardiovascular diseases, diabetes, hemoglobinopathies, hypertension, infectious diseases, inflammation, metabolic syndrome, neurological diseases, obesity, and skin diseases. However, due to its weak solubility and bioavailability, it has limited potential as an oral medication. Numerous factors including low water solubility, poor intestinal permeability, instability at alkaline pH, and fast metabolism contribute to curcumin's limited oral bioavailability. In order to improve its oral bioavailability, different formulation techniques such as coadministration with piperine, incorporation into micelles, micro/nanoemulsions, nanoparticles, liposomes, solid dispersions, spray drying, and noncovalent complex formation with galactomannosides have been investigated with in vitro cell culture models, in vivo animal models, and humans. In the current study, we extensively reviewed clinical trials on various generations of curcumin formulations and their safety and efficacy in the treatment of many diseases. We also summarized the dose, duration, and mechanism of action of these formulations. We have also critically reviewed the advantages and limitations of each of these formulations compared to various placebo and/or available standard care therapies for these ailments. The highlighted integrative concept embodied in the development of next-generation formulations helps to minimize bioavailability and safety issues with least or no adverse side effects and the provisional new dimensions presented in this direction may add value in the prevention and cure of complex chronic diseases.



1. INTRODUCTION

Chronic diseases including autoimmune diseases, cancer, cardiovascular diseases, diabetes, hepatocellular, neurological, and renal diseases have persistent high incidence and fatality rates worldwide.[1,2] Finding feasible treatment strategies are challenging due to the high prevalence of these diseases and the involvement of several pathways in their development, including JAK/STAT3, JNK, NF-κB, MEK/ERK, p38/MAPK, and PI3K/Akt/mTOR, etc.[1−10] Therefore, classical monotarget therapies are insufficient to treat these diseases. Besides, the cost of contemporary pharmaceuticals is high, and have several unfavorable side effects.[7,10,11] Indeed, there is an increasing need for the development of safer, effective, multitargeted, and cost-effective therapeutic regimens to replace the current harmful and ineffective treatment approaches. A growing body of preclinical and clinical evidence suggests that natural substances derived from diverse plants are potential therapeutic candidates against a wide range of fatal chronic conditions, and their alternative formulations can be employed to boost the bioavailabilities of these substances.[2,7,10,12−14]

The perennial herb turmeric, *Curcuma longa* Linn. belongs to the Zingiberaceae family, is indigenous to South Asia's tropical areas. The rhizomes of this plant have been used for centuries as a remedy for several diseases in the Indian (Ayurveda) and Chinese Medicinal Systems.[15−17] Curcumin is a bioactive phytochemical derived from this rhizome. It has traditionally been used as a spice, food preservative, and coloring ingredient.[15,18] The chemical name for curcumin is diferuloylmethane ($C_{21}H_{20}O_6$) and the IUPAC name is (1*E*-6*E*)-1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione with a molecular weight of 368.37 g/mol and melting point of 183 °C. The two aryl rings in curcumin are symmetrically connected to a β-diketone moiety by ortho-methoxy phenolic groups.[17−21] A pH-dependent keto-enol

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tautomerism appears in curcumin wherein the stable enol form predominates in an alkaline medium and a keto form in acidic and neutral conditions.[17] In addition, curcumin's color varies depending on the pH level, yielding a brilliant yellow solution between 2.5 and 7.0, and turning to dark red when the pH rises over that level.[17,20]

Currently, there are several curcumin-based products available in the market, including pills, ointments, capsules, and cosmetics.[16,22−24] Turmeric and curcumin have been the established remedies for various ailments, primarily as antiatherosclerotic, antibacterial, anticancerous, antifungal, anti-inflammatory, antioxidant, antithrombotic, and antiviral agents.[22,25,26] Additionally, a comprehensive analysis of the literature identified curcumin as one of the excellent natural compounds that exhibit analgesic, antirheumatic effects, hypoglycemia, hypolipidemia, hepatoprotective, nephron protective, pulmonoprotective, and cardioprotective activities.[18,21,27−35] Besides, in vitro studies have shown that curcumin modulates several cell signaling pathways, upregulates p53, p21, and p27, downregulates cell survival gene products, and induces apoptosis.[15,36−39] Numerous clinical studies have demonstrated its outstanding safety, tolerability, and effectiveness even at higher oral dosages, and is currently being sold as a dietary supplement in several countries across the world.[27,28,40,41] Curcumin has not yet been authorized as a drug despite its excellent efficacy and safety, and a key issue for this is the relative bioavailability of curcumin. Research over the last three decades has revealed the poor gut absorption, rapid metabolism, and systemic elimination of curcumin that significantly restricts its bioavailability.[18,23,42−44] Moreover, curcumin is a hydrophobic molecule with a log*P* of ∼3.2 (octanol-water partition coefficient), making it practically water-insoluble (with a water solubility of only 30 nM).[21,45−47] Curcumin activity has a reported half-life of 10 min in a phosphate buffer of pH 7.4 which further limits its clinical use.[46,47] Even after consuming high amounts of conventional curcumin, very low levels of plasma curcumin were detected. Hence, the overarching goal of all strategies is to increase curcumin's solubility and bioavailability.[48−52] Numerous approaches have been used to improve the solubility and subsequently the bioavailability of curcumin including curcumin-piperine complex, curcumin nanoparticles or nanomicelles, liposomal curcumin, phospholipidated curcumin, and phytosomal curcumin complex.[18,42,44,47,53,54] Therefore, in the current review, we provide an overview of the bioavailability, safety, tolerability, and efficacy of various curcumin formulations in clinical trials. We have extensively reviewed the completed clinical trials on curcumin formulations of different generations and highlighted their efficacy in treating several chronic diseases. Significant variations in research design, volunteer race, dose, duration, and route of administration were noted. Moreover, we discussed the advantages and limitations of these formulations and highlighted the future perspectives from the podium to clinical practice.

2. BIOAVAILABILITY OF CONVENTIONAL CURCUMIN

The major findings from curcumin research are the observation of noticeably low serum levels, limited tissue distribution, rapid metabolism, inactive metabolite formation, and rapid clearance/elimination from the body.[18,42,47,48,55] Several studies have shown that administration of a large amount of pure curcumin yielded only a trace amount of serum levels of curcumin in rats owing to its poor absorption from the gut.[55−60] Curcumin administered orally at 2 g/kg to rats showed a maximum serum concentration of only 1.35 ± 0.23 μg/mL at 0.83 h, whereas the same dosage showed undetectable or extremely low serum levels, i.e., 0.006 ± 0.005 μg/mL at 1 h.[55] Similarly, in another clinical trial, it was shown that administration of 3.6 g of curcumin by the oral route generated serum levels of only 11.1 nmol/L after 1 h.[51] More recently, Yang and colleagues demonstrated that curcumin given intravenously (10 mg/kg) produced a maximum serum level of 0.36 ± 0.05 g/mL, whereas a 50-fold increase in dosage of oral supplement produced only a maximum serum level of 0.06 ± 0.01 g/mL in rats.[56] Besides, following oral treatment of 400 mg of curcumin in rats, Ravindranath et al. demonstrated that only residues of the unmodified substance were discovered in the liver and kidney.[59] This study also showed that 90% of curcumin was noted in the stomach and small intestine at 30 min while only 1% of curcumin was present after 24 h.[59] Another study revealed that administration of radiolabeled (tritium or H^3) curcumin at 10, 80, and 400 mg doses resulted in the detection of a considerable amount of curcumin in tissues of rats administered with only 400 mg after 12 days.[58] Also, the percentage of absorbed curcumin remained constant irrespective of the dosage indicating the dose-independent limitations to bioavailability in these animals.[58] Similarly, supplementation of 450−3600 mg of curcumin daily for a week before surgery to patients with colorectal cancer metastases to liver showed no curcumin in their liver tissues.[61] In phase II clinical trial on patients with advanced pancreatic cancer, an oral dose of 8 g/day curcumin resulted in only 22−41 ng/mL of plasma concentration.[62] Further, orally given curcumin (2 g/kg) to rats had an absorption half-life of 0.31 ± 0.07 and elimination half-life of 1.7 ± 0.58 h, albeit in humans, the same dose did not enable the measurement of these shelf life values since most of the levels were below the detection limit at almost all the periods.[55]

These studies indicated that the method of administration (whether oral or intravenous) affects the serum levels of curcumin and further suggest that the serum achievable concentrations of curcumin in humans and rats are not exactly comparable. Hence, it is not only imperative to develop bioavailable curcumin but also equally important to find the safety and efficacy of these formulations in humans.

3. METHODOLOGY

A literature search was carried out using "curcumin and clinical trials" in two different databases, Pubmed and Scopus, until June 2022. Around 458 articles appeared in PubMed and 3622 articles appeared in Scopus for the mentioned keyword. The studies that appeared were analyzed thoroughly for the mentioned keywords.

The inclusion criteria applied to select the relevant studies were (a) clinical studies that have used various generations of curcumin formulation; (b) studies on human subjects (both healthy and diseased); (c) full-text manuscripts in English. The exclusion criteria were (a) preclinical studies; (b) studies on the pure form of curcumin; (c) full-text not in English; (d) in silico studies; (e) conference abstracts; (f) review articles; (g) meta-analysis; and (h) case reports. All the relevant articles as per these criteria are included in the table, figures, and text.

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Table 1. Composition of Various Curcumin Formulations That Are Tested Clinically[a]

curcumin formulation	composition	ref
First-Generation Formulation		
active ingredients formulated as soft gel capsules	fish oil 250 mg, phosphatidyl choline concentrated sunflower oil 150 mg, silymarin 75 mg, choline bitartrate 35 mg, curcumin 35 mg, D-α-tocopherol 10 mg for a total of 830 mg	122
ArtemiC oral spray (1 mL)	6 mg artemisinin, 20 mg curcumin, 15 mg frankincense, 60 mg vitamin C	127
BCM-95	*Curcuma longa* extract with essential oils from turmeric rhizome, rice flour, vegetable cellulose, vegetable stearate, silica	116
bioactive capsules	rutin (500 mg), 1.5 g fish oil (18% EPA and 7% DHA), 500 mg curcumin (95% curcuminoids)	128
C3 complex bioperine	curcuminoid extract containing curcumin, desmethoxycurcumin, bisdesmethoxycurcumin and piperine formulation	51,61
CartiJoint Forte	curcumin (BCM-95), chondroitin sulfate and glucosamine hydrochloride	123
Coltect tablet	curcumin 500 mg, green tea 250 mg, and selenium 100 μg	130
CUC-1	300 mg solution of curcumin	129
CuraMed	552−578 mg of BCM-95 extracted in ethanol 99% (v/v) and 100% ethyl acetate +49−52 mg volatile oil from *C. longa* containing 22−23.4 mg aromatic turmerone + inactive excipients (120−140 mg) including phosphatidyl choline, medium chain TGs, glycerol, gelatin, yellow beeswax	124
Curamin	350 mg BCM-95 + 150 mg of *Boswellia serrata* Roxb. ex Colebrgum resin extract corresponding to 75% boswellic acids and 10% 3-*O*-acetyl-11-keto-boswellic acid	124
Curcugreen	Dry rhizomes of turmeric extracted with ethyl acetate to form turmeric oleoresin, precipitated and combined with turmeric essential oil	126
Curcumall	A tincture of curcumin C3 95%, turmeric and ginger dissolved in glycerin and 0.4% alcohol	131
curcumin chitosan mouthwash	Purified curcuminoid powder 0.1 g (79:19:1 of curcumin/dimethoxycurcumin/bisdemethoxycurcumin) dissolved in 40 mL PEG, 25 mL of 2% low molecular weight chitosan	87
curcumin capsules from Theravalues Corporation, Tokyo, Japan	10% curcumin, 2% other curcuminoids, 3.2% gum ghatti, 0.27% citric acid, 54.53% dextrin, and 30% maltose	133
curcumin forte	95% curcumin plus 5% piperine	86
curcuminoid turmeric matrix formulation	50% Total curcuminoids (41.2% curcumin, 7.3% desmethoxycurcumin, 1.5% bisdemethoxycurcumin), 3% essential oil, 2% protein, 40% total carbohydrate	138
curcuminoid turmeric oil formulation	440 mg curcuminoid (347 mg curcumin, 84 mg desmethoxycurcumin, 9 mg bisdemethoxycurcumin), 38 mg of turmeric oil	139,140
Cureit/Acumin	46.5% Total curcuminoids (36% curcumin, 9.0% desmethoxycurcumin, 1.5% bisdemethoxycurcumin), 43% total carbohydrates, 5% fiber, 2.4% proteins, 3.2% volatile oil containing aromatic turmerone, dihydroturmerone, turmeronol, curdione, bisacurone	135
Infla-Kine	Proprietary blend of *Lactobacillus fermentum* extract, burdock seed, zinc, lipoic acid, papaya enzyme, BCM-95	144
Killox	190 mg curcuminoids, 20 mg resveratrol, 100 mg NAC, 6 mg zinc with the formulation of enterosoma technology to obtain increased bioavailability	146
LCD capsule	Soft gel capsules containing lutein (20 mg), curcumin (200 mg total curcuminoids), zeaxanthin (4 mg) from marigold flower extract, algal source vitamin D3 (600 IU), medium chain triglyceride oil, linseed oil, olive oil, sunflower lecithin, tocopherol and thyme oil	147
natural product capsule by Vitacost	Each 500 mg capsule contain 150 mg curcumin, 75 mg resveratrol, 150 mg epigalloatechin-3-gallate, 125 mg soy isoflavone	148
Nutrafol women's capsules	A proprietary blend of clinically tested and bio-optimized phytoactive extracts, vitamins, minerals and botanicals; major ingredients include standardized extracts of Ashwagandha, curcumin, piperine, capsiacin, hydrolyzed marine collagen, hyaluronic acid, organic kelp, saw palmetto, tocotrienol rich tocotrienol/tocopherol complex	153
PureVida	460 mg of fish oil (DHA and EPA), 125 mg of Hytolive powder (12.5 mg of hydroxytyrosol), 50 mg of curcumin extract (47.5 mg of curcuminoids)	150
Reglicem	Chromium picolinate 100 μcg Cr, 200 mg curcumin dry extract, 200 mg berberine dry extract, 300 mg inositol, 40 mg banaba dry extract with 1% corosolic acid, silicon dioxide, magnesium stearate, dicalcium phosphate, microcrystalline cellulose	151
Turmix tablet	300 mg curcumin plus 5 mg piperine	113
Turmix mouthwash	*C. longa* dry extract 0.1% w/v standardized to 95% curcumin (tetrahydrocurcumin) along with thymol, eucalyptol, clove oil, mentha oil, tea tree oil	113
Volatile oil formulation of curcumin	85.9% curcuminoids (70.2% curcumin, 14.3% demethoxycurcumin, 1.4% bisdemethoxycurcumin), 7−9% essential oil naturally present in turmeric	135
WEC (hot water extract of curcumin)	*C. longa* rhizomes were crushed and incubated with hot water. The supernatant was concentrated, mixed with dextrin and spray-dried to obtain powder. The powder was later dissolved in dimethyl sulfoxide	152
Second-Generation Formulation		
Actbiome	curcumin and asafetida complex was incorporated on to turmeric dietary fiber by spray drying process with complete natural matrix via polar−nonpolar sandwich technology	154
Algocur (Meriva formulation)	each tablet contains 1 g of Meriva	199

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Table 1. continued

curcumin formulation	composition	ref
Second-Generation Formulation		
BioCurc/CLDM	85% curcumin, 13% demethoxycurcumin, 2% bisdemethoxycurcumin, lauryl macrogol-32 glycerides, polysorbate-20, DL-α-tocopherol, hydroxyprolyl cellulose	155
CartiJoint Forte	Chondroitin sulfate, glucosamine hydrochloride, BCM-95	
CHC (curcumin formulation with hydrophilic carrier)	Novel water-soluble formulation containing turmeric extract 20−28%, a hydrophilic carrier 63−75%, cellulose derivatives 10−40%, natural antioxidants 1−3%	157
CSL	curcumin/soy lecithin/microcrystalline cellulose in the ratio of 1:2:2	137
curcumin nanomicelle gel from Sina Pharmaceuticals	1% curcumin nanomicelle gel	264
curcuminoid cream from GPO Thailand	Tetrahydrocurcuminoid in phosphatidyl choline liposomes	202
curcuminoid micelles	7% native curcumin powder containing 82% curcumin, 16% demethoxycurcumin and 2% bisdemethoxycurcumin and 93% Tween-80 filled in Licaps; finally, each capsule contained 20.1 mg curcumin, 3.9 mg demethoxycurcumin, and 0.5 mg bisdemethoxycurcumin	160,161,163
Curserin	200 mg curcumin, 120 mg phosphatidylserine, 480 mg phosphatidylcholine and 8 mg piperine from *Piper nigrum* L. dry extract	159
CW8	curcumin in complex with γ-cyclodextrin	137
FLAVOMEGA	fructose, phospholipidic curcumin, acetyl carnitine-HCL, ascorbic acid, flavoring, coenzyme Q10, Skullcap, Baicalin, green tea catechins, antiagglomerant, acesulfame potassium, sucralose	164
Flexofytol	bio-optimized curcumin 42 mg mixed with polysorbate Tween-80	165,166
HydroCurc	80% curcumin, 17% demethoxycurcumin, 3% bisdemethoxycurcumin, entrapped in LipiSperse delivery system	167
Ialuril soft gel tablets	Oral food integrator containing curcumin, quercetin, hyaluronic acid and chondroitin sulfate	145
Meriva	curcumin complexed with phosphatidyl choline	179
NE65	Lipoid S LPC65 (5% w/w), olive oil (20% w/w), potassium sorbate (0.1% w/w) and distilled water	200
NLC65	Lipoid S LPC65 (5% w/w), olive oil (2.22% w/w), precirol ATO5 (7.77% w/w) and distilled water	200
NLC80	Lipoid S LPC80 (5% w/w), olive oil (2.22% w/w), precirol ATO5 (7.77% w/w) and distilled water	200
phospholipid curcumin formulation	19.8% curcuminoids (16.1% curcumin, 3.2% demethoxycurcumin, 0.5% bisdemethoxycurcumin), 40% phospholipids, 40% microcrystalline cellulose	135
phospholipidated curcumin	∼20% curcumin and soy phosphatidyl choline in 1:2 weight ratio, 2 parts of microcrystalline cellulose	204
theracurmin	curcumin dispersed in colloidal nanoparticles- Gum ghatti obtained from exudation of ghatti trees was dissolved in water and mixed with curcumin powder and glycerin, wet grinded and dispersed as colloidal nanoparticle by a high-pressure homogenizer	282,283
theracurmin beverage	Water, sugar syrup (high-fructose corn syrup, sugar), cinnamon extract, ginger, alanine, acidulant, Theracurmin, vitamin C, flavor, sweetner (licorice, sucralose), niacinamide, calcium pantothenate, vitamin B6, vitamin B2, vitamin B1, vitamin B12	286
Third-Generation Formulation		
curcumagalactomannosides	Novel oral delivery for of curcumin prepared using noncovalent complex formation between curcumin and fenugreek galactomannans	301
curcuRouge	Amorphous formulation of curcumin, modified starch, corn-starch containing 37 w/w% of curcumin	297
Curcuwin Ultra+	63−75% polyvinyl pyrrolidine, 10−40% cellulosic derivatives, 1−3% natural antioxidants, 20−28% turmeric extract	47,304
Longvida	curcumin in solid lipid formulation containing proprietary blend of vegetable derived stearic acid dextrin, hydroxypropyl methylcellulose, soy lecithin, ascorbyl palmitate, silicon dioxide	306,308

[a]Abbreviation: CLDM, Curcumin liquid droplet micromicellar formulation; DHA, Docosahexaenoic acid; EPA, icosapentaenoic acid; HCl, Hydrogen chloride.

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4. CURCUMIN FORMULATIONS

The straightforward ways to address the limitation(s) of curcumin are to enhance its bioavailability, shield it from oxidation and metabolism, and increase its ability to target diseased tissues and/or organs.[18,47] One of the main strategies for increasing curcumin's bioavailability is to utilize adjuvants that can inhibit or delay its metabolism.[18,63] Other intriguing innovative formulations that appear to offer longer circulation, improved permeability, and resistance to metabolic processes include liposomes, micelles, nanoparticles, and phospholipid complexes.[18,42,64] These bioavailable or bioenhanced formulations of curcumin are generally categorized into three different formulations. The classic example of first-generation formulation includes the use of significant amounts of adjuvants such as piperine from black pepper, turmeric oils, or any other natural compounds that were included to inhibit the essential detoxification enzymes such as hepatic aryl hydrocarbon hydroxylase, cytochrome P450, mixed-function oxygenases, and UDP-glucuronyltransferase.[18,63,65,66] The first-generation formulation enhances the absorption time of curcumin by inhibiting or delaying its metabolism. The formulations such as curcumin−piperine, C3 complex−piperine (C3 complex/bioperine), turmeric fiber or oil with curcumin, BCM-95, and Cureit belong to the first-generation category.[44] In the second-generation, emulsifiers such as carbohydrate complexes, polyethoxylated hydrogenated castor oil, lipid complexes, phospholipid complexes, polysorbates, water-dispersible nanopreparations, and spray drying were used to increase the solubility of curcumin. These included BioCurc, Cavacurcmin, CurcuWIN, Hydrocurc, Meriva, Nanocurcumin, Novasol, Theracurmin, and Turmipure Gold.[44] Although increases in plasma curcuminoids levels occur primarily through their conjugated metabolites (glucuronides and sulfates), numerous studies have shown that these conjugated metabolites lack biologically significant effects because of the large size, quick renal elimination, limited membrane, and blood−brain barrier (BBB) permeability.[44,67,68] For this reason, delivering curcumin in its free form (naturally unconjugated) is essential to maximize its therapeutic effects. The third-generation curcumin formulations including Longvida and CurQfen have solved the issue of "free" curcuminoids bioavailability, membrane permeability, and cellular uptake without the use of artificial emulsifiers like polysorbates.[44] This section details the clinical safety and efficacy of all three generations of curcumin formulations. Different formulations and their composition are listed in Table 1.

4.1. First-generation curcumin formulation. Early attempts to increase absorption of curcumin included the addition of turmeric oil (BCM-95; BioCurcumax; Curcugreen), a small amount of piperine (curcumin C3 complex) to stimulate the gastrointestinal system, prevent curcumin efflux and inhibit hepatic and intestinal glucuronidation, or as a turmeric oleoresin (Curcugen).[18,44,55] All of these formulations have shown incremental improvement in curcumin absorption and efficacy clinically (Table 2, Figure 1). For instance, supplementation with curcumin/piperine (500 mg-2g/day curcumin plus 5−20 mg/day piperine) formulation resulted in a significant reduction in ubiquitin, muscle atrophy F box (MAFbx)/atrogin-1, chymotrypsin-like protease, interleukin 2 (IL-2), TNF-α, INF, IL-6, IL-10, and enhancement in bioavailability, safety, tolerability, and delayed onset of muscle soreness in healthy subjects without adverse side effects.[55,69,70]

In patients with arsenic-induced oxidative stress, this formulation effectively decreased DNA damage, ROS generation, lipid peroxidation, and improved antioxidant capacity.[71] In another study, the administration of curcumin (1.5 mg/day) and piperine (5 mg/day) for 2 months resulted in the efficient alleviation of IL-6 and improvement in forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and asthma control test scores in bronchial asthma patients compared to those who received regular asthma drugs.[72] Moreover, this formulation (1−1.5 g/day curcumin with 5 mg/day piperine) reduced the symptoms including weakness, dry cough, sore throat, sputum cough, ague muscular pain, headache, dyspnea, deterioration, and hospitalized duration in COVID-19 patients without side effects.[73,74] Besides, the treatment with this formulation significantly improved mouth opening flexibility, cheek flexibility, and tongue protrusion capacity and suppressed burning sensation in oral submucous fibrosis (OSF) patients compared to placebo (starch and lactose capsules).[75] In another randomized placebo-controlled trial, this formulation was shown to effectively augment GSH levels and decrease erythrocyte MDA levels in pancreatitis patients with no adverse side effects.[76] In addition, it also reduced leptin and TNF-α levels and increased adiponectin levels in T2D patients over 12 weeks of treatment.[77] Curcumin formulation with piperine and ginger ameliorated erythrocyte sedimentation rate (ESR), tender joint count (TJC), swelling joint count (SJC), disease activity score (DAS), and relieved pain and inflammation in rheumatoid arthritis patients.[78] Another study demonstrated that curcumin along with piperine and taurine remarkably suppressed IL-10, AST, ALT, α-L-fucosidase, and miR-21 levels and improved overall survival in hepatocellular cancer patients.[79] Another curcumin/piperine tablet containing other ingredients including propranolol, aliskiren, cilazapril, celecoxib, aspirin, and metformin for 10 weeks enhanced the median survival rate in glioblastoma patients.[80] This treatment was also found to be safe with minimal side effects including indigestion and marginal bradycardia (propranolol effect).[80] Another study employed two tablets of curcumin−spirulina−*Boswellia* extract (each tablet with 400 mg curcumin, 50 mg spirulina, and 50 mg *Boswellia* extract) to patients with benign thyroid nodules and reported the reduced nodule area without adverse side events.[81] Also, curcumin and fennel essential oil (FEO) tablets (2 capsules, a total of 84 mg curcumin with 50 mg FEO) caused substantial relief in symptoms and improved quality of life in inflammatory bowel syndrome (IBS) patients.[82] Moreover, the administration of three Oxy-Q tablets (each tablet containing 480 mg curcumin with 20 mg quercetin) repressed polyp size and number without side effects in familial adenomatous polyposis patients (FAP).[83] In another study, a novel curcumin formulation administered as 2 capsules per day (each capsule containing 30 mg curcumin, 100 mg bovine lactoferrin, 15 mg zinc acetate, 100 mg lysolecithin), 600 mg *N*-acetylcysteine (NAC), and 20 mg pantoprazole inhibited serum pepsinogens, decreased disease severity and improved the cure rate in patients infected with *Helicobacter pylori* (*H. pylori*).[84] In addition, rectal suppositories of 350 mg curcumin and 80 mg *Calendula* extract (1 suppository/die, for 1 month) significantly inhibited inflammation compared to those who received a placebo suppository (identical to treatment) without side effects.[85] Yet another formulation, Curcumin Forte (95% curcumin plus 5% piperine formulation) remarkably increased positive and negative symptoms scale

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Table 2. Effect of Curcumin Formulations on Various Human Diseases[a]

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
First-Generation Formulation							
active ingredients formulated as soft gel capsules	NAFLD	126	3 months	2 capsules/day	↑cholesterol, ↑glucose, ↓AST	safe, well-tolerated, no adverse side effects	122
ArtemiC oral spray	COVID-19	50	day 1 and day 2	twice daily	↑clinical improvement, ↑SpO2 normalization, ↓O_2 supplementation, ↓fever, ↓hospital stay	no adverse side effects, safe, well-tolerated	127
BCM-95	healthy volunteers	11		2g	↑bioavailability and retention time compared to curcumin−lecithin and piperine formulation	safe, no adverse side effects	117
	multiple myeloma	33	28 days	8 g/day	↑overall remission, ↓NFκB, ↓TNF-α, ↓VEGF, ↓IL-6		118
	multiple sclerosis	80	24 months	1 g/day	↓combined unique active lesions	no serious adverse side effects	119
	NAFLD	50	12 weeks	1.5g/day	↑physical activity, ↓hepatic fibrosis, ↓TNF-α, ↓NF-κB, ↓AST, ↓ALT	safe, well-tolerated, no adverse side effects	120
	prediabetes	84	90 days	500 mg/day	↑HDL, ↓BMI, ↓weight, ↓TC, ↓TG, ↓LDL, ↓ non-HDL-C	no serious adverse side effects	121
bioactive capsule + WPI	age-related sarcopenia	41	12 weeks	7 capsules + 20 g	↑knee extension strength, ↑gait speed	no serious adverse side effects	128
C3 complex + bioperine	healthy volunteers	10		12 g + 60 mg	no significant effect	safe	40
	MetS	117	8 weeks	1 g/day + 10 mg/day	↓LDL-C, ↓non-HDL-C, ↓TC, ↓TG, ↓LPA, ↑HDL-C	safe, well-tolerated, no serious adverse side effects	92
		117	8 weeks	1 g/day + 10 mg/day	↑SOD, ↓MDA, ↓CRP, ↓glucose, ↓HbA1c, ↓SBP, ↓DBP	safe	93
		117	8 weeks	1 g/day + 10 mg/day	↓TNF-α, ↓TGF-β, ↓IL-6, ↓MCP-1	safe, well-tolerated, no serious adverse side effects	94
		117	8 weeks	1 g/day + 10 mg/day	↑adiponectin, ↓leptin	well-tolerated	95
	NAFLD	70	12 weeks	500 mg + 5 mg	↑TIBC, ↓hematocrit, ↓ESR, ↓AST, ↓ALT, ↓ALP, ↓TC, ↓LDL-C, ↓iron, ↓Hb	no adverse side effects	96
		55	8 weeks	500 mg + 5 mg	↓weight, ↓severity, ↓TNF-α, ↓MCP-1, ↓EGF	no serious adverse side effects	97
		55	8 weeks	500 mg/day + 50 mg/day	no significant on PAB	no serious adverse side effects	112
	obesity	30	30 days	1 g/day + 10 mg/day	↓TG	safe, well-tolerated, no serious adverse side effect	98
		30	2 weeks	1 g/day + 10 mg/day	↓PAB		105
		30	4 weeks	1 g/day + 10 mg/day	↑Zn/Cu		106
		30	4 weeks	1 g/day + 10 mg/day	↓IL-1β, ↓IL-4, ↓VEGF		107
	osteoarthritis	40	6 weeks	1.5 g/day + 15 mg/day	↑SOD, ↑GSH, ↓MDA, ↓oxidative stress		91
		53	6 weeks	1.5 g/day + 15 mg/day	↓IL-4, ↓IL-6, ↓hs-CRP, ↓TGF-β		108
	SM-induced chronic pruritus	96	4 weeks	1 g/day + 10 mg/day	↑GPx, ↑SOD, ↑CAT, ↓Sp, ↓VAS, ↓pruritus severity, ↓DLQI scores	safe, no serious adverse side effects	99
		96	4 weeks	1 g/day + 10 mg/day	↓IL-8, ↓hs-CRP, ↓CGRP		109
	SM-intoxicated with pulmonary complications	78	4 weeks	1.5 g/day + 15 mg/day	↓FEV1, ↓FVC, ↓IL-6, ↓IL-8, ↓TNF-α, ↓TGF-β, ↓MCP-1, ↓Sp, ↓hs-CRP, ↓CGRP	safe, well-tolerated, no serious adverse side effects	89
		89	4 weeks	1.5 g/day + 15 mg/day	↑GSH, ↑CpAT score ↓MDA, ↓symptoms, ↓SGRQ	safe	110
	T2D	100	3 months	500 mg/day + 5 mg/day	↓glucose, ↓C-peptide, ↓HbA1c, ↓ALT, ↓AST	no adverse side effects	90
		118	12 weeks	1 g/day + 10 mg/day	↑HDL-C, ↓TC, ↓non-HDL-C, ↓LPA, ↓weight, ↓BMI, ↓TG	no adverse side effects	111
	TBI	62	7 days	500 mg/day + 5 mg/day	↓leptin	well-tolerated, no serious adverse side effects	100
		62	7 days	500 mg/day + 5 mg/day	↑GPx, ↓IL-6, ↓CRP, ↓MCP-1, ↓TNF-α, ↓SOFA score, ↓APACHE II, ↓NUTRIC score	safe, no adverse side effects	101

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
First-Generation Formulation							
C3 complex + piperine	PMS	76	10 days/3 CMC	500 mg + 5 mg	↑vitamin D, ↓AST, ↓DB	no serious adverse side effects	102
		124	10 days/3 CMC	500 mg + 5 mg	↓PSST score, ↓dysmenorrhea pain	no serious adverse side effects	103
	T2D	118	8 weeks	1 g/day + 10 mg/day	↑TAC, ↑SOD, ↓MDA	safe, no serious adverse side effects	104
CartiJoint Forte	osteoarthritis	53	6 weeks	1.5g/day	↓VAS score, ↓WOMAC score	no adverse side effects	123
CUC-1 paclitaxel	metastatic breast cancer	150	12 weeks	300 mg/week (i.v.) + 80 mg/m^2	↑ORR, ↑physical performance	anemia, grade 3−4 side effects occurred in 5 patients	129
Coltect tablet	ulcerative colitis index	20	8 weeks	2 tablets/day	↑remission rate, ↓Clinical activity	safe, tolerated	130
CuraMed	osteoarthritis	201	12 weeks	1.5 g/day	↑Physical performance, ↑pain relief, ↑40 m walking speed ↓pain index, ↓stiffness, ↓degree of difficulty to move knee joint, ↓pain on standing from chair, ↓time taken to rise from chair, ↓time taken to ascend or descend from the stairs, ↓WOMAC index	safe, tolerated	124
	periodontitis	76	7 days	200 mg	↓postoperative discomfort, ↓pain	no adverse side effects	125
CuraMin	osteoarthritis	201	12 weeks	1.5 g/day	↑physical performance, ↑pain relief, ↑40 min walking speed, ↓WOMAC index, ↓pain index, ↓stiffness, ↓degree of difficulty to move knee joint, ↓pain on standing from chair, ↓time taken to rise from chair, ↓time taken to ascend or descend from the stairs	safe, tolerated	124
Curcugreen	obesity	84	90 days	500 mg/day	↑physical activity, ↓BMI, ↓FPG, ↓HbA1c, ↓insulin	no serious adverse side effects	126
Curcugreen + zinc	obesity	84	90 days	500 mg/day + 30 mg/day	↑Insulin sensitivity, ↓BMI, ↓FPG, ↓insulin resistance	no serious adverse side effects	126
Curcumall	OLP	7	21 days	20 drops/day		no adverse side effects	131
curcumin amorphous formulation	NAFLD	80	8 weeks	500 mg/day	↓liver fat content, ↓BMI, ↓TC, ↓LDL-C, ↓TG, ↓AST, ↓ALT, ↓glucose, ↓glycated Hb	safe, well-tolerated, no serious adverse side effects	132
curcumin capsule (from Theravalues Corporation)	exercise-induced oxidative stress	10	2 h before exercise ±2 h after exercise	90, 180 mg	↑BAP, ↑GSH, ↑CAT, ↓d-ROMs		133
curcumin forte (Solgar)	schizophrenia	38	24 weeks	3 g/day	↑PANSS score, ↓CDSS scores	no adverse side effects	86
curcuminoid-chitosan mouthwash	denture stomatitis	30	2 weeks	3 × 10 mL/day	↑anti-*Candida* activity, complete response in 80% patients	no adverse side effects	87
Cureit/Acumin	aged adults	30	3 months	500 mg	↑handgrip strength, ↑weight-lifting capacity, ↑distance covered ↓time taken to walk the same distance	no serious adverse side effects	134
	healthy volunteers	45	single dose	500 mg	exhibited greater bioavailability than phospholipid formulation and volatile oil formulation	no adverse side effects	135
		30	single dose	500 mg	↑VO2 max, ↓CK, ↓VAS score, ↓DOMS occurrence	no adverse side effects	136
CEO (essential oil formulation)	healthy subjects	12		376 mg	↑absorption	no adverse side effects	137
CW8 (γ-cyclodextrin formulation)	healthy subjects	12		376 mg	↑absorption	no adverse side effects	137
curcuminoid turmeric matrix formulation	RA	36	90 days	500 mg/day 1000 mg/day	↑ACR response, ↓VAS score, ↓DAS score ↓ESR, ↓CRP, ↓RF values, ↓swollen joints, ↓tender joints	no serious adverse side effects	138
curcuminoid turmeric oil formulation	T2D	53	10 weeks	1500 mg/day	↑adiponectin, ↓TG, ↓hs-CRP		139
		53	10 weeks	1500 mg/day	↓mean weight, ↓BMI, ↓waist circumference, ↓FBS	no adverse side effects	140
curcumin alcohol gel	psoriasis	10	4 weeks	1% gel	↓PhK activity, ↓TRR, ↓severity of parakeratosis, ↓CD8+ T cells		141
curcumin gel	OSF	60	6 weeks	3 or 4x 5 mg/day	↓burning sensation, ↑mouth opening capacity	safe, nontoxic	142
	OSF	40	4 weeks	2% gel	↓burning sensation, ↓LDH, ↑mouth opening capacity	safe, noninvasive, no adverse side effects	143

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
First-Generation Formulation							
curcumin mucoadhesive patch	OSF	40	4 weeks	2% gel	↓burning sensation, ↓LDH, ↑mouth opening capacity	safe, noninvasive, no adverse side effects	143
curcumin + *Boswellia* + spirulina	benign thyroid nodules	34	12 weeks (3 visits with 6 week interval)	800 + 100 + 100 mg/day	↓benign thyroid nodules	no adverse side effects	81
CU-FEO (curcumin + fennel essential oil)	IBS	121	30 days	84 mg +50 mg	↑symptom relief, ↑QoL ↓severity score, ↓abdominal pain	safe, well-tolerated, no adverse side effects	82
curcumin + piperine	healthy volunteers	8	single dose	2 g+20 mg	↑bioavailability no adverse side effects	safe, well-tolerated,	55
	recreationally active subjects	23	11 days	2 g/day +20 mg/day	↑DOMS time, ↓Ubiquitin, ↓MAFbx/atrogin-1, ↓chymotrypsin-like protease		69
	healthy subjects	16	7 days	500 mg/day +20 mg/day	↓IL-2, ↓TNF-α, ↓IFN, ↓IL-6, ↓IL-10		70
	arsenic-induced oxidative stress	286	3 months	1g/day	↑antioxidant capacity, ↓DNA damage, ↓ROS generation, ↓lipid peroxidation		71
	bronchial asthma	40	2 months	2 × 750 mg/day +5 mg/day	↓IL-6, ↑FEV1, ↑FVC, ↑ACT score		72
	COVID-19	140	14 days	2x(525 mg+2.5 mg)	↑O_2 saturation, ↓symptoms, ↓deterioration, ↓hospitalized duration	safe, no serious adverse side effects	73
	COVID-19	46	14 days	2x(500 mg+5 mg)/day	↓weakness, ↓dry cough, ↓sore throat, ↓sputum cough, ↓ague, ↓muscular pain, ↓headache, ↓dyspnea	no serious adverse side effects	74
	OSF	90	6 months	600 mg/day	↑mouth opening flexibility, ↑tongue protrusion, ↑cheek flexibility, ↓burning sensation	no adverse side effects	75
	pancreatitis	20	6 weeks	500 mg/day +5 mg/day	↑GSH, ↓erythrocyte MDA levels	no adverse side effects	76
	T2D	118	12 weeks	1 g/day +10 mg/day	↑adiponectin, ↓leptin, ↓TNF-α, ↓leptin/adiponectin ratio		77
curcumin + piperine + ginger	RA	60	8 weeks	-	↓TJC, ↓ESR, ↓SJC, ↓DAS score, ↓inflammation, ↓pain	no serious adverse side effects	78
curcuminoids + piperine + taurine	hepatocellular cancer	20	3 cycles 30 days each	4 g + 40 mg +500 mg/day	↑OS, ↑albumin, ↓IL-10, ↓miR-21, ↓AST, ↓ALT, ↓AFU		79
curcuminoids + piperine	healthy volunteers	8	2 days	16 g + 96 mg	no significant effect on paracetamol metabolization		115
Oxy-Q (curcumin + quercetin)	FAP	5	6 months	1440 mg/day +60 mg/day	↓polyp number, ↓polyp size	no serious adverse side effects	83
curcumin tablet lactoferrin + *N*-acetylcysteine + pantoprazole	*H. pylori*$^+$ with dyspepsis	25	7 days	60 mg+200 mg+ 1200 mg +40 mg/day	↑cure rate, ↓overall severity, ↓serum pepsinogens		84
curcumin extract + *Calendula* extract	CP/CPPS III	55	1 month	350 mg +80 mg	↓inflammation	no adverse side effects, well-tolerated	85
curcumin + propranolol + aliskiren + cilazapril + celecoxib + piperine + aspirin + metformin	glioblastoma	10	10 weeks	-	↑median survival	minimal adverse effects, safe	80
Ialuril soft gel tablets	endometriosis	20	12 weeks	2 pills/day	↓dysmenorrhea, ↓chronic pelvic pain, ↓dysuria	no adverse side effects	145
Infla-Kine	healthy volunteers	24	4 weeks	2 capsules/day	↑QoL, ↓IL-6, ↓IL-8, ↓NF-κB, ↓TNF-α		144
Killox	TURP, TURB, and BPH	80	10−60 days	Once/day	↓postoperative and late complications, duration of irritation	well-tolerated, no adverse side effects	146
LCD capsule	dry eye syndrome	60	8 weeks	1 tablet/day	↑Schirmer's strip wetness length, ↑tear volume, ↑TBUT score, ↑SPEED score, ↓OSDI score, ↓corneal and conjunctival staining score, ↓tear osmolarity, ↓MMP-9 positive score	safe, no adverse side effects	147

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
First-Generation Formulation							
MEC	RA with chronic periodontitis	45	6 weeks	2 × 10 mL/day	↓ESR, ↓RF, ↓CRP, ↓ACPA, ↓PI, ↓PD, ↓CAL	well-tolerated	88
NAIOS	ME/CFS	76	15.2 ± 4.81 months	-	↓IgM-mediated autoimmune response to OSEs and NO- adducts, ↓FF score, ↓severity of illness		149
NP capsule by Vitacost	healthy volunteers	11	2 weeks	1 g/day	↓TNF-α induced NF-κB activation	safe, well-tolerated	148
Nutrafol women's capsule	women with self-perceived hair thinning	40	6 months	4 capsules/day	↑number of terminal and vellus hairs, ↑hair growth, ↑quality, ↑volume, ↑thickness	no serious adverse side effects, safe, well-tolerated	153
PureVida	breast cancer	45	1 month	3 capsules/day	↓CRP, ↓pain score	no serious adverse side effects	150
Reglicem	fasting dysglycemia	148	3 months	1 tablet/day	↓FBS, ↓PPBS, ↓HbA1c, ↓insulin, ↓HOMA-index, ↓TG, ↓TC, ↓CRP	no serious adverse side effects	151
Turmix tablet	OSF	147	12 weeks	3 times a day	↑mouth opening flexibility, ↑tongue protruding capacity, ↓burning sensation		113
	OSF		12 weeks	900 mg/day	↑mouth opening flexibility, ↓burning sensation	no adverse side effects	114
Turmix tablet + Turmix mouthwash	OSF	147	12 weeks	3 times a day +2 times a day	↑tongue protruding capacity, ↑mouth opening flexibility, ↓burning sensation		113
WEC	healthy subjects	47	8 weeks	0.75 g	↑H_2O content of the skin, ↓TEWL	no serious adverse side effects	152
WEC + curcumin	healthy subjects	47	8 weeks	0.75 g + 30 mg	↑H_2O content of the skin, ↓TEWL	no serious adverse side effects	152
Second-Generation Formulation							
Actbiome	healthy subjects	30	8 weeks	2 × 250 mg/day	↑fecal bifidobacteria, ↑fecal lactobacilli, ↑ideal stool form and frequency, ↓IL-10, ↓GSRS score	no adverse side effects	154
Algocur	men rugby players with osteo-muscular pain	50	10 days	2 tablets/day	↑physical function, ↑adherence to treatment, ↓pain, ↓VAS score	safe, well-tolerated	199
BioCurc/CLDM	healthy volunteers	15	48 h (14 days wash out period)	6 capsules (64.6 mg)	↑absorption, ↑bioavailability	safe, no adverse side effects	155
cavacurcumin + ω-3 FA + astaxanthin + GLA + tocotrienols + hydroxy tyrosol + vitamin D3 + potassium	healthy volunteers	80	4 weeks	500 mg +675 mg +3 mg+9.5 mg+ 12.5 mg+6.25 mg +1000 IU + 12.5 mg	↑brachial flow mediated dilation, ↑EPA, ↑ω-3 FA index, ↓hs-CRP, ↓SBP	no adverse side effects, well-tolerated	156
cCHC	healthy volunteers	12	4 trials separated by 7 days each	376 mg	↑absorption compared to CS, CP, CTR	no adverse side effects	157
	diabetic macular edema	73	6 months	2 tablets/die	↓CRT, ↓inner retinal layer thickness	safe, no adverse side effects	158
CSL (phytosomal formulation)	healthy subjects	12		376 mg	↑absorption	no adverse side effects	137
curcumin phosphatidyl choline + Irinotecan	solid tumors	23	28 days	1, 2, 3 and 4 g/day + 200 mg/m^2	↑delay in disease progression	no toxicity, tolerated leukopenia, nausea, fatigue, diarrhea	41
Curserin	obesity	80	8 weeks	800 mg/day	↑HDL-C, ↓FPG, ↓FPI, ↓GGT, ↓HOMA-IR, ↓GOT, ↓GPT, ↓LAP, ↓FLI, ↓TG, ↓non-LDL-C, ↓HSI	no adverse side effects	159
curcuminoid micelles	healthy subjects	42	6 weeks (4 weeks wash out phase)	294 mg/day	↑Bioavailability	safe and well-tolerated GI side effects	160
	MI	110	single dose	480 mg	↓raise of CK-MB		163
FLAVOMEGA	DMD, FSHD, LGMD	29	24 weeks	80 g/day	↑muscle performance, ↑global strength, ↑lower limb strength, ↑isokinetic knee extension, ↑6 min walk distance, ↓CK, ↓ROS, ↓valine, ↓FFA	no adverse side effects, well-tolerated	164
Flexofytol	osteoarthritis	22	3 months	6 capsules/day	↓Coll2−1, ↓CRP, ↓global disease assessment activity	well-tolerated, no serious side adverse	165

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
Second-Generation Formulation							
Flexofytol + *Boswellia* extract + pine bark extract + methylsulfonyl methane	osteoarthritis	106	12 weeks	168 mg/day +250 mg/day +100 mg/day +1500 mg/day	↓activity impairment, ↓FIHOA score	no serious adverse side effects	166
iron + HydroCurc	healthy subjects	155	6 weeks	18 mg +500 mg/day 65 mg +500 mg/day	↓TBARS, ↓TNF-α, ↓GI side effects, ↓fatigue, ↓IL-6	no adverse side effects	167
HydroCurc + maltodextrin	healthy and young males	28	single dose	500 mg+500 mg	↑IL-6, ↑IL-10, ↓DOMS pain, ↓TC, ↓capillary lactate and LDH		168
lecithinized curcumin	MetS	120	6 weeks	1 g/day	no effect on vitamin E, ↓vitamin E/LDL, ↓vitamin E/TC, ↓vitamin E/TG	no serious adverse side effects	170
Lipocurc	locally advanced or metastatic tumors	32	8 weeks	100, 300 mg/m^2	↓PSA, ↓CEA, ↓CA 19−9	well-tolerated, anemia, hemolysis	169
Meriva	healthy subjects	9		209, 376 mg of curcuminoids	↑absorption		173
	healthy subjects	12	7 days	2 g/day	↑absorption	no serious adverse side effects	174
	CKD	24	3 or 6 months	1000 mg/tablet	↓MCP-1, ↓IL-4, ↓IFNγ, ↓TBARS, ↓P-cresyl sulfate, ↓carbohydrate intake, ↓protein intake, ↓total fiber intake, ↓phosphorus and potassium intake, ↓*Escherichia-Shigella*, ↓*Enterobacter verrucomicrobia*, ↓*Firmicutes*, ↑*Lachnoclostridium* spp., ↑*Lachnospiraceae* family, ↑*Lactobacillaceae* spp., ↑Prevotellaceae	no adverse side effects	175
	diabetes with microangiopathy	50	4 weeks	1 g/day	↑PO_2, ↓skin flux, ↓edema	well-tolerated	176
		77	4 weeks	1 g/day	↑visual acuity, ↑microcirculation, ↓retinal edema, ↓peripheral edema	well-tolerated	177
	diabetic macular edema	11	3 months	1 g/day	↓macular edema	no adverse side effects	195
	Gulf War illness	39	every 30 ± 3 days four times	1 or 4 g day	↓symptom severity	no serious adverse side effects	178
	hypercholesterolemia	76	4 weeks	1 g/day	↓TC, ↓LDL-C, ↓TC/HDL ratio	no adverse side effects	179
	MetS	120	6 weeks	1 g/day	↑zinc, ↑zinc/copper ratio		180
	NAFLD	102	8 weeks	1 g/day	↓TC, ↓TG, ↓LDL-C, ↓non-HDL-C, ↓uric acid	safe, well-tolerated	181
		102	8 weeks	1 g/day	↑hepatic vein flow, ↓portal vein diameter, ↓liver volume ↓BMI, ↓waist circumference, ↓AST, ↓ALT	safe, well-tolerated	182
		36	8 weeks	1.5 g/day	↑hepatic vein flow, ↓NAFLD severity, ↓BMI, ↓TC, ↓LDL-C, ↓non-HDL-C, ↓TG, ↓portal vein diameter, ↓Liver size, ↓AST, ↓ALT, ↓serum uric acid, ↓HDL	safe, well-tolerated	183
		58	8 weeks	250 mg/day	↓3-methyl-2-oxovaleric acid, ↓3-hydroxyisobutyrate, ↓citrate, ↓kynurenine, ↓succinate, ↓α-ketolgutarate, ↓methylamine, ↓yrimethylamine, ↓hippurate, ↓indoxyl sulfate, ↓taurocholic acid ↓chenodeoxy cholic acid, ↓lithocholic acid,		193
		65	8 weeks	250 mg/day	↑HDL-C, ↑adiponectin, ↓leptin	safe, no side effects	194
		54	8 weeks	250 mg/day	↓MLH1, ↓MSH2, ↓weight, ↓waist circumference, ↓hip circumference, ↓BMI	safe, well-tolerated, no serious adverse side effects	184
	osteoarthritis	50	12 weeks	1 g/day	↑walking distance in treadmill, ↓WOMAC score, ↓CRP, ↓distal edema, ↓hospitalization, ↓usage of anti-inflammatory drugs	no adverse side effects	185
		100	8 months	1 g/day	↑Karnofsky scale score, ↓stiffness, ↓WOMAC score, ↓negative effects on social function, ↓IL-1β, ↓IL-6, ↓ESR, ↓sCD40L, ↓sVCAM-1, ↑distance covered on treadmill	excellent tolerability, safe	186
	pancreatic cancer	44	until death	2 g/day 28 days cycle	↑response rate, ↑stable disease period, ↑OS, ↑PFS	safe	187
	prostatic hyperplasia	61	24 weeks	1 g/day	↑QoL, ↓signs and symptoms, ↓urinary infections and block	no adverse side effects	188
	psoriasis	63	12 weeks	2 g/day	↓IL-22, ↓PASI	safe and well-tolerated	189
	risk of T2D	29	12 weeks	1 g/day	↓GSK-3β, ↓IAPP, ↓insulin resistance ↓risk of Alzheimer's disease	no adverse side effects	190

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
Second-Generation Formulation							
	solid tumors	96	8 weeks	900 mg/day	↑QoL, ↓IL-6, ↓TNF-α, ↓TGF-β, ↓Sp, ↓hs-CRP, ↓CGRP, ↓MCP-1 ↓IL-8	safe and well-tolerated, no serious adverse side effects	191
	solid tumors with radio- and chemotherapy-induced side effects	158	4 months	500 mg/day	↓burden of side effects	no serious adverse side effects	192
Meriva + fish oil	healthy subjects	16	4 days separated by a week of out period	180 mg +2 capsules	↓PPBS, post- prandial insulin		196
Meriva + anthocyanin	colorectal adenomatous polyposis	35	4−6 weeks	1 g/day +1g/day	↓NFκB, ↓Ki67	no serious adverse side effects	198
Meriva + phytosterol	hyper-cholesterolemia	70	4 weeks	200 mg/day +2 g/day	↓TC, ↓LDL-C	no adverse side effects	179
		82	4 weeks	228 mg/day +2.3 g/day	↓TC, ↓LDL-C, ↓TC:HDL-C ratio, ↓CVD risk, ↓LDL-P number	safe	197
micellar curcumin formulation (beverage)	glioblastoma	13	4 days	3 × 70 mg	↑bioavailability, ↑inorganic phosphate, ↓PCr/Pi ratio, ↑intratumoral pH	no serious adverse side effects	162
nanocurcumin (curcumin nanomicelle from Exir Nano Sina company)	amylotrophic lateral sclerosis	54	12 months	80 mg/day	↑survival	safe, no adverse side effects	218
	ankylosing spondylitis	24	4 months	80 mg/day	↓RORγ t, ↓IL-17, ↓IL-23, ↓miR-141, ↓miR-155, ↓miR-200, ↓symptoms		219
	Behcet's disease	36	8 weeks	80 mg/day	↑Treg cells, ↑RNAs of FOXP3, ↑TGF-β, ↑IL-10, ↑miR-25, ↑miR-106b	no adverse side effects	237
	bladder cancer	26	4 weeks	160 mg/day	↑clinical response	well-tolerated	246
	CAD	80	3 months	80 mg/day	↓MMP-9, ↓MMP-2	safe	220
	COVID-19	40	14 days	160 mg/day	↓mRNA and serum IL-6, mRNA and serum IL-1β, ↓serum IL-18		238
	COVID-19	60	2 weeks	4 soft gels/day	↑lymphocyte count, ↓symptoms	no adverse side effects	221
	COVID-19	41	2 weeks	160 mg/day	↑oxygen saturation, ↓symptoms, ↓symptom resolution time, ↓lymphocyte count, ↓hospitalized duration	no serious adverse side effects	243
	COVID-19	80	21 days	160 mg/day	↑Treg cell frequency, ↑FOXP3, ↑IL-10, ↑IL-35, ↑TGF-β		239
	COVID-19	40	2 weeks	160 mg/day	↑IL-4, ↑FOXP3, ↓IFNγ, ↓TBX21	no adverse side effects	240
	COVID-19	80	21 days	160 mg/day	↓RORγ t, ↓IL-17, ↓IL-21, ↓IL-23, ↓GM-CSF, ↓symptoms, ↓Th17 count, ↓hospitalized duration ↓mortality rate,		241
	COVID-19	60	7 days	240 mg/day	↓mortality rate, ↓IFNγ, ↓TNF-α ↓IL-6, ↓IL-1β	safe and tolerable	242
	COVID-19	48	6 days	160 mg/day	↑O_2 saturation, ↓symptoms, ↓LOS	no adverse side effects	222
	diabetic foot ulcer	60	12 weeks	80 mg/day	↑TAC, ↑Insulin sensitivity, ↑GSH, ↓FPG, ↓insulin, ↓TC, ↓LDL-C	safe, no serious adverse side effects	248
	diabetes on HD	60	12 weeks	80 mg/day	↑TAC, ↑TN, ↑PPARγ, ↑LDLR, ↓TC, ↓LDL-C, ↓VLDL-C, ↓MDA, ↓TC/HDL-C, ↓hs-CRP, ↓insulin, ↓TG, ↓FPG,	no adverse side effects	249
	DSPN	80	8 weeks	80 mg/day	↓HbA1c, ↓FBS, ↓total reflex score, ↓total neuropathy score, ↓waist circumference, ↓temperature,	safe, well-tolerated	252
	gingivitis	50	4 weeks	80 mg/day	↓MGI, ↓PBI	no adverse side effects	261
	hemodialysis	54	3 months	120 mg/day	↓serum IL-6 and TNF-α, ↓mRNA IL-6 and TNF-α		291
	HNC	32	6 weeks	80 mg/day	↑OM development duration, ↓OM severity	no adverse side effects	223
	infertility	60	10 weeks	80 mg/day	↑sperm count, ↑sperm concentration, ↑sperm motility, ↑TAC, ↑testosterone, ↓MDA, ↓CRP, ↓TNF-α, ↓FSH, ↓LH, ↓PRL	no adverse side effects	229
	MetS	50	12 weeks	80 mg/day	↓TG, ↓HOMA-β		230
		50	12 weeks	80 mg/day	↑adiponectin, ↑TAC, ↓MDA	no serious adverse side effects	253
	migraine	44	2 months	80 mg/day	↓MCP-1, ↓headache attack frequency, ↓headache severity and duration	no adverse side effects	255

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
Second-Generation Formulation							
		100	8 weeks	80 mg/day	↓frequency, severity, duration of headache	no adverse side effects	256
		80	2 months	80 mg/day	no significant effect on VCAM		257
		80	2 months	80 mg/day	↓headache frequency, ↓IL-1β	no adverse side effects	258
	NAFLD	84	3 months	80 mg/day	↑HDL, ↑QUICKI, ↑Nesfatin, ↓fatty liver degree, ↓AST, ↓ALT, ↓FBS, ↓FBI, ↓HbA1c, ↓TG, ↓TC, ↓LDL, ↓HOMA-IR, ↓TNF-α, ↓IL-6, ↓hs-CRP	no adverse side effects	254
	oral mucositis	50	7 weeks	160 mg/day	↓pain score, ↓severity		262
	OLP	57	1 month	80 mg/day	↓pain, ↓lesion, ↓burning sensation	no adverse side effects	247
	osteoarthritis	30	3 months	80 mg/day	↑Treg cells, ↓VAS score, ↓CRP, ↓$CD4^+$ and CD8 T^+ cells, ↓Th 17 cells, ↓B cells	no adverse side effects	226
		30	3 months	80 mg/day	↓miR-155, ↓miR-138, ↓miR-16		236
	Parkinson's disease	60	9 months	80 mg/day	↓MDS-UPDRS part III score	well-tolerated, mild GI symptoms	231
	prostate cancer	64	3 days before RT and during RT	120 mg/day	↓radiation-induced proctitis	well-tolerated, no serious adverse side effects	224
	RA	65	12 weeks	120 mg/day	↓DAS score, ↓TJC, ↓SJC	no adverse side effects	225
	RRMS	25	6 months	80 mg/day	↓Th17 cells, ↓RORγ t, ↓IL-17		259
		50	6 months	-	↑miR-15a, ↑miR-19b, ↑miR-106b, ↑miR-320a, ↑miR-363, ↑miR-31, ↑miR-181c, ↑miR-150, ↑miR-340, ↑miR-599, ↓miR-17-92, ↓miR-16, ↓miR-27, ↓miR-29b, ↓miR-126, ↓miR-128, ↓miR-132, ↓miR-155, ↓miR-326, ↓miR-550	no systemic adverse effects	232
		50	6 months	80 mg/day	↑Treg cells frequency, ↑FOXP3, ↑IL-10, ↑TGF-β		260
	schizophrenia	64	16 weeks	80, 160 mg/day	↑response rate, ↓PANSS positive subscale, ↓PANSS negative subscale score, ↓CGI-S, ↓CGI-I, ↓PANSS general psychopathology subscale score, ↓total PANSS score	safe, no serious adverse side effects	233
	sepsis	40	10 days	160 mg/day	↓PCT, ↓IL-6, ↓TNF-α, ↓duration of mechanical ventilation, ↓SOFA		244
		40	10 days	160 mg/day	↓MDA, ↓IL-18, ↓IL-1β, ↓ICAM-1, ↓TC, ↓VCAM-1, ↓ IL-6, ↓TLR-4, ↓Bax, ↓FBS, ↓TG, ↓ALT, ↓ALP, ↓GGT, ↓bilirubin, ↓creatinine, ↓prealbumin, ↓SOFA score, ↓duration of ventilation, ↑IL-10, ↑CAT, ↑SOD, ↑TAC, ↑Bcl-2, ↑Nrf-2, ↑TLC		245
		14	10 days	160 mg	↓ESR, ↓IL-8, ↓neutrophils, ↓platelets, ↓Presepsin, ↓WBCs	no adverse side effects	227
	T2D	40	8 weeks	80 mg/day (with endurance training)	↓FBG, ↓glycated Hb, ↓insulin		250
	T2D associated polyneuropathy	80	8 weeks	80 mg/day	↓depression, ↓anxiety	safe, well-tolerated	251
	thyroid cancer undergone thyroidectomy	21	10 days	160 mg/day	↓micronuclei in lymphocyte	safe, no adverse side effects	228
	ulcerative colitis	56	4 weeks	240 mg/day	↓score for urgency of defecation, ↓SCCAI score	no serious adverse side effects	235
nanocurcumin (from Theravalues Corp. Japan)	MetS	44	6 weeks	80 mg/day	↑IL-10, ↑BDNF, ↑TAC, ↓IL-6, ↓MDA, ↓hs-CRP		265
nanocurcumin	breast cancer	42	2 weeks	80 mg/day	↓RISR severity, ↓pain		266
nanocurcumin	migraine	38	2 months	80 mg/day	↓Pentraxin 3		267
		80	2 months	80 mg/day	↓IL-6 mRNA, ↓IL-6, ↓hs-CRP	no adverse side effects	268
		40	2 months	80 mg/day	↓IL-17, ↓IFNγ	no adverse side effects	269
nanocurcumin (prepared using wet milling technique)	RA	10	8 months	20 mg/L and 50 mg/L	↓inflammation		270
nanocurcumin + ω-3 fatty acids	migraine	72	2 months	-	↓attack frequency, ↓ICAM-1		271

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
Second-Generation Formulation							
		74	2 months	80 mg/day +2.5 g/day	↓TNF-α, ↓attack frequency	no adverse side effects	272
		80	2 months	80 mg/day +2.5 g/day	↓IL-6 mRNA, ↓IL-6, ↓hs-CRP	no adverse side effects	268
		74	2 months	80 mg/day +1800 mg/day	↓COX-2, ↓iNOS, ↓frequency, severity and duration of headache		273
		80	2 months	80 mg/day	↓VCAM, ↓headache severity and frequency		257
		80	2 months	80 mg/day	↓headache frequency, ↓IL-1β	no adverse side effects	258
nanocurcumin + acetretin	psoriasis	15	12 weeks	3 g/day +0.4 mg/kg /day	↓PASI	no serious adverse side effects	274
nanocurcumin + coenzyme Q10	migraine	100	8 weeks	80 mg/day +300 mg/day	↑MSQ score, ↓frequency, severity, duration of migraine, ↓MIDAS score, ↓HIT-6 score	no adverse side effects	256
nanocurcumin + *Nigella sativa* oil	postmenopausal women	120	6 months	80 mg +1 g	↑miR-21	no serious adverse side effects	275
nanocurcumin mouthwash	HNC oral mucositis	74	6 weeks	0.1%	↑delayed onset, ↓risk of OM, ↓severity	no adverse side effects	276
curcumin nanomicelle gel from Sina (Iran)	OLP	31	4 weeks	1%	↑efficacy index, ↓REU score	well-tolerated, no adverse side effects	263
	RAS	48	1 week	3 × 1%/day	↑efficacy index, ↓lesion size, ↓pain score	no adverse side effects	264
curcumin nanomicelle from Minoo Pharmaceuticals Co. with resistance training	NAFLD	45	12 weeks	80 mg/day	↓AST, ↓ALT		277
nanogel 2% curcumin	chronic periodontitis	45	45 days	2% gel	↓*Aggregatibacter actinomycetemcomitans*, ↓*Tannerella forsythia*, ↓*Porphyromonas gingivalis*		278
curcumin nanoparticle	periodontitis	20	15 days	50 μg	↑*Veillonella parvula*, ↑Actinomyces spp., ↓PPD, ↓CAL, ↓BOP, ↓IL-6, ↓*Porphyromonas gingivalis*	no adverse side effects	279
NE 65	healthy subjects	15	4 weeks	0.125 g	↓skin surface permittivity, ↓NMF		200
NLC 65	healthy subjects	15	4 weeks	0.125 g	↑TEWL, ↓NMF, ↓skin surface permittivity, ↓urea		200
NLC 80	healthy subjects	15	4 weeks	0.125 g	↑TEWL, ↓skin hydration, ↓skin surface permittivity, ↓NMF, ↓urea		200
phospholipidated curcumin	MetS	120	6 weeks	1 g/day	no significant improvement in pro- and antioxidant balance		204
		120	6 weeks	1 g/day	↓saturated fatty acid intake		205
		120	6 weeks	1 g/day	↓severe anxiety	no serious adverse side effects	206
		80	6 weeks	1 g/day	no significant effect on BMI, waist circumference, and serum cathepsin D levels		207
phospholipidated curcuminoids	MetS	120	6 weeks	1 g/day	no significant effect		208
phytosomal curcumin	MetS	81	6 weeks	1 mg/day	no considerable effect on aryl esterase activities		203
curcuminoid cream from GPO, Thailand	focal or generalized vitiligo	10	12 weeks	Twice daily	↑repigmentation	safe, well-tolerated, minor adverse side effects	202
Theracurmin	non demented adults	46	18 months	180 mg/daymonths	↑verbal and visual memory, ↑attention, ↓depression, ↓FDDNP	Four subjects complained abdominal pain, gastritis, nausea and one subject complained heat and pressure in chest	280
	aged adults	40	18 months	180 mg/day	↑improved SRT, ↑visual memory ↑attention, ↓neurodegeneration	safe	281
	healthy subjects	14	single dose	30 mg	↑plasma concentration of curcumin, ↑alcohol intoxication, ↓acetaldehyde	no adverse side effects	282
	healthy subjects	6		150 mg, 210 mg	↑absorption, ↑bioavailability curcumin, ↑alcohol intoxication, ↓acetaldehyde	safe, no serious adverse side effects	283
	healthy subjects	9		182.4 ± 1.0 mg	↑absorption and bioavailability than BCM-95 and Meriva	no adverse side effects	116
	healthy subjects	14	4 weeks	300 mg/day	↑MVC torque recovery, ↓CK		284

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
Second-Generation Formulation							
	healthy subjects	10	7 days before exercise	180 mg/day	↓IL-8, ↓inflammation		288
	healthy subjects	10	7 days after exercise	180 mg/day	↑MVC torque, ↑ROM, ↓muscle soreness, ↓CK activity		288
	Crohn's disease	30	12 weeks	360 mg/day	↑clinical response rate, ↑lesion healing, ↓endoscopic disease severity	no serious adverse side effects	290
	COPD	48	24 weeks	180 mg/day	↓AT-LDL	safe, no serious adverse side effects	293
	exercise-induced muscle soreness	24	7 days before and 4 days after exercise	180 mg/day	↑ROM, ↓muscle soreness		287
	osteochondral diseases	50	12 months	180 mg/day	↑JOA score, ↑VAS, ↑JKOM, ↓roughness in lateral compartment of femur, ↓stiffness of knee cartilage	no serious adverse effects	292
	postmenopausal women	56	8 weeks	150 mg/day	↓brachial SBP	no adverse side effects	289
	noninsulin dependent DM	33	6 months	180 mg/day	↓rise in oxidized LDL, ↓TG, ↓γ-GTP		294
theracurmin + exercise	postmenopausal women	45	8 weeks	150 mg/day	↓brachial and aortic SBP, ↓radial AIx, ↓DBP	no adverse side effects	289
theracurmin solution	pancreatic or biliary duct cancer	16	>9 months	200−400 mg/day		no adverse side effects	285
theracurmin beverage	healthy subjects	24		30 mg/100 mL	↑absorption efficiency	no adverse side effects	286
valdone curcumin soft gel	ulcerative colitis	69	6 weeks	100 mg/day	↑clinical response rate, ↑clinical remission rate	no serious adverse side effects	201
Third-Generation Formulation							
curcumin galactomannan formulation	healthy subjects	18	30 days	1000 mg/day	↑α- and β-waves of EEG, memory improvement, ↓α/β ratio, audio-reaction time, ↓choice based-visual reaction time		302
	osteoarthritis	80	84 days	400 mg/day	↑walking performance, ↓VAS ↓stiffness score, ↓IL-1β, ↓VCAM	safe	298
CurQfen	occupational stress	60	30 days	1000 mg/day	↑QoL, ↑CAT, ↑SOD, ↑GPx, ↑GSH, ↓TBARS, ↓fatigue, ↓lipid peroxidation	safe, no serious adverse side effects	299
	obesity	22	12 weeks	500 mg/day	↑HDL, ↓homocysteine	no adverse side effects	300
	osteoarthritis	84	6 weeks	400 mg/day	↑improvement in walking, ↑physical activity, ↓VAS score, ↓WOMAC score, ↓stiffness score, ↓hs-CRP, ↓IL-1β, ↓IL-6, ↓sVCAM	no serious adverse side effects	301
curcuRouge	aged adults	40	4 weeks	180 mg/capsule	↓WBC count, ↓neutrophil count, ↓neutrophil/lymphocyte	no safety issues	303
curcuwin Ultra+	healthy subjects under fasting	24		250, 500 mg	↑bioavailability	no safety issues	304
Longvida	aged adults	60	12 weeks	400 mg/day	↑mood-related benefits, ↓fatigue ↑cognitive benefits	safe, well-tolerated	305
	aged adults	80	12 weeks	400 mg/day	↑working memory performance ↓fatigue score, ↓tension, ↓anger, effects	no serious adverse side	306
	middle aged and older adults	39	12 weeks	2000 mg/day	↑vascular NO bioavailability, flow-mediated dilation, ↑NO-dependent dilation	safe, well-tolerated ↓oxidative stress, ↑brachial artery	307
	healthy subjects	38	4 weeks	80 mg/day	↑CAT, ↑MPO, ↑NO scavenged radicals, ↓TG, ↓salivary amylase, ↓ALT, ↓Aβ protein, ↓ICAM		308
	Alzheimer's disease	8	2 × 20 g/day	2 days	↑detection of amyloid spots in retina		314
	obesity	134	16 weeks	160 mg/day	↑cerebrovascular responsiveness		309
		152	16 weeks (160 mg/day curcumin)	800 mg	no significant effect on arthritis	no serious adverse side effects	310
	OSF	30	3 months	2 g/day	↑mouth opening capacity, ↓burning sensation		312
	osteoarthritis effects	50	90 days	2 × 400 mg/day	↓VAS score, ↓WOMAC score	no serious adverse side	313

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Table 2. continued

curcumin formulation	disease/condition	no. of patients	duration	dose	outcome	adverse effect (if any)	ref
Third-Generation Formulation							
Longvida + fish oil	obesity	152	16 weeks	800 mg/day + 400 mg/day EPA + 2 g/day DHA	↑HDL-C, ↓HR, ↓TG ↓cerebral artery stiffness	no serious adverse side effects	311
	obesity	134	16 weeks	800 mg/day + 400 mg/day EPA + 2 g/day DHA	↑cerebrovascular responsiveness 400 mg/day EPA + 2 g/day DHA		309

[a]Abbreviations: Aa, *Aggregatibacter actinomycetemcomitans*; ACPA, Anticitrullinated protein antibody; ACR, American College of Rheumatology; ACT, Asthma control test; ADPKD, Autosomal dominant polycystic kidney disease; AFU, Alpha-L-fucosidase; ALDH, Aldehyde dehydrogenase; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AOPPs, Advanced oxidation protein products; APACHE II, Acute physiology, and chronic health 370 evaluation II; AST, Aspartate aminotransferase; BALP, Bone-specific alkaline phosphatase; BANA, *N*-benzoyl-DL-arginine-2-naphthylamide; BAP, Biological antioxidant potential; BAX, Bcl-2 associated X-protein; BCL-2, B-cell lymphoma 2; BDNF, Brain-derived neurotrophic factor; BMD, Bone mineral density; BMI, Body mass index; BOP, Bleeding on probing; BPH, Benign prostatic hyperplasia; BSE, Boswellia serra extract; BVAS, Birmingham vascular activity score; CA 19−9, Carbohydrate antigen 19−9; CAL, Clinical attachment level; CAT, Catalase; CD40L, Cluster of differentiation 40 ligand; CD133, Cluster of differentiation 133; CDAI, Crohn's disease activity index; CDSS, Calgary depression scale for schizophrenia; CEA, Carcinoembryonic antigen; CFU, Colony forming unit; CGI-I, Clinical global impressions-improvement score; CGI-S, Clinical global impressions-severity score; CGRP, Calcitonin gene related peptide; CK, Creatinine kinase; CKD, Chronic kidney disease; CK-MB, Creatinine kinase, MB fraction; CLDM, Curcumin liquid droplet micellar formulation; CLDQ, Chronic liver disease questionnaire; CMC, Consecutive menstrual cycle; Coll2−1, Serum type 2 collagen peptide; COPD, Chronic obstructive pulmonary disease; COX-2, Cyclooxygenase 2; COVID-19, Coronavirus disease 2019; CP, Curcumin phytosome formulation; CpAT, COPD assessment test; CRP, C-reactive protein; CRT, Central retinal thickness; CS, Standardized curcumin; CTR, Curcumin formulation with volatile oils of turmeric rhizome; CTx, C-terminal cross-linking telopeptide of type I collagen; Cu, Copper; CUA, Combined unique activity; Cur, Curcumin; CVD, cadiovascular disease; CXCl1, CXC motif chemokine ligand 1; DAS, Disease activity score; DASS-21, Depression, anxiety, stress scale-21; DB, Direct bilirubin; DBP, Diastolic blood pressure; dFLC, Difference between clonal and nonclonal free-light chain; DFP, Deferiprone; DLQI, Dermatology life quality index; DMD, Duchenne muscular dystrophy; DNA, Deoxyribonucleic acid; DOMS, Delayed onset muscle soreness; DSPN, Diabetic sensorimotor polyneuropathy; EEG, Electroencephalogram; EGF, Epidermal growth factor; EPA, Eicosapentanoic acid; ESR, Erythrocyte sedimentation rate; FA, Fatty acid; FEV, Forced expiratory volume; FF score, Fibromyalgia and fatigue rating score; FFA, Free fatty acids; FDDNP, -(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile; FIHOA, Functional index for hand osteoarthritis; FLC, Free-light chain; FLI, fatty liver index; FLIP, FLICE inhibitory proteins; FMD, Brachial artery flow-mediated dilation; FOXP3, Forkhead box P3; FPG, Fasting plasma glucose; FPI, fasting plasma insulin; FSH, Follicular stimulating hormone; FSHD, Facioscapulohumeral dystrophy; FVC, Forced vital capacity; GGT, Gamma-glutamyl transferase; GI, Gingival index; GLA, Gamma linoleic acid; GM-CSF, Granulocyte-macrophage colony stimulating factor; GOT, Glutamate-oxaloacetate transaminase; GPT, Glutamate pyruvate transaminase; GPx, Glutathione peroxidase; GSH, Glutathione; GSK-3β, Glycogen synthase kinase-3 beta; GSRS, Gastrointestinal symptom rating scale; GTP, Guanosine triphosphate; H_2O, Water; H_2O_2, Hydrogen peroxide; HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; Hb, Hemoglobin; HbA1c, Hemoglobin A1c; HDL, High density lipoprotein; HDL-C, HDL-cholesterol; HDR, Headache daily results; HIT-6, Headache impact test 6; HNC, Head and neck cancer; HOMA-β, Homeostatic model assessment for pancreatic beta cell function; HOMA-IR, Homeostatic model assessment for insulin resistance; hs-CRP, High-sensitivity C-reactive protein; HSC, Hematopoietic stem cell; HSI, Hepatic steatosis index; HTLV-1, Human lymphotropic virus type-1; IAPP; Islet amyloid polypeptide; IBD, Inflammatory bowel disease; IBS, Inflammatory bowel syndrome; ICAM, Intracellular adhesion molecule; IgM, Immunoglobulin M; IFN, Interferon; iFLC, Involved free-light chain ratio; IFNγ, Interferon gamma; IIEF-5, 5-item version of the international index of erectile function; IL, Interleukin; iNOS, Inducible nitric oxide synthase; IPSS, International prostate symptom score; IPSS-S, International prostate symptom score-storage sub score; IPSS-V, International prostate symptom score-voiding sub score; IR, Insulin resistance; JKOM, Japanese knee osteoarthritis measure; JOA, Japanese orthopedic association, LAP, Lipid accumulation, product; LDH, Lactate dehydrogenase; LDL, Low density lipoprotein; LDL-C, LDL cholesterol; LDLR, LDL receptor; LDSI, liver disease symptom index; LGMD, Limb girdle muscular dystrophy; LH, Leutinizing hormone; LNAA, Large neutral amino acids; LOS, Length of hospital stay; LPA, Lipoprotein A; LV, Left ventricular; MAFbx, Muscle atrophy F-box; ME/CSF, Myalgic encephalomyelitis/chronic fatigue syndrome; MCP-1, Monocyte chemoattractant protein-1; MDA, Malondialdehyde; MDS-UPDRS, Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; MELD, Model for end-stage liver disease; MetS, Metabolic syndrome; MGI, Modified gingival index; MHb, Methemoglobin; MI, Myocardial infarction; MIDAS, Migraine disability assessment; MIF, Monocyte inhibitory factor; miRNA, Micro RNA; MLH1, MutL homologue 1; MMP, Matrix metalloproteinase; MN, Micronuclei; MPO, Myeloperoxidase; MSM, Methylsulfonyl methane; MSH2, MutS homologue 2; MSQ, Migraine-specific quality of life; MVC, Maximal voluntary contraction; NAC, *N*-acetylcysteine; NAFLD, Nonalcoholic fatty liver disease; NAIOS, Nutraceuticals with anti-inflammatory, oxidative and nitrosative stress; NF-κB, Nuclear factor kappa B; NLC, Nanostructured lipid carriers; NMF, Natural moisturizing factor; NO, Nitric oxide; NO-adducts, Nitroso-adducts; NP, Nanoparticle; Nrf2, Nuclear factor erythroid 2-related factor 2; NTBI, Nontransferrin bound iron; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; NUTRIC, Nutrition risk in critically ill; OLP, Oral lichen planus; OM, Oral mucositis; ORR, Objective response rate; OS, Overall survival; OSDI, Ocular surface disease index; OSE, Oxidative specific epitopes; OSF, Oral submucous fibrosis; PAB, Pro-oxidant antioxidant balance; PANSS, Positive and negative symptoms scale; PASI, Psoriasis area severity index; PBE, Pine bark extract; PBI, Papillary bleeding index; PCI, percutaneous coronary intervention; PCOS, Polycystic ovary syndrome; PCr/Pi, Phosphocreatine to inorganic phosphate ratio; PCS, P-cresyl sulfate; PCT, Procalcitonin; PD, Pocket depth; PDT, Photodynamic therapy; PFS, Progress free survival; PGC-1α, Peroxisome proliferator and activated γ receptor coactivator 1 alpha; PGE2, Prostaglandin E2; PI, Plaque index; PhK, Phosphorylase kinase; Pg, *Porphyromonas gingivalis*; PMS, Premenstrual syndrome; PPARγ, Peroxisome proliferator-activated receptor gamma; PPBS, Postprandial blood sugar; PPD, Probing pocket depth; ppFEV$_1$, Predicted forced expiratory volume in one second; PPFT, Periprostatic fat thickness; PON1,

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Table 2. continued

paraoxonase-1; PRL, Prolactin; PSA, Prostate-specific antigen; PSQI, Pittsburgh sleep quality index; PSST, PMS screening tool; PTH, Parathyroid hormone; PV, Prostatic volume; Q_{max}, maximum flow rate; QoL, Quality of life; QUICKI, quantitative insulin sensitivity check index; RA, Rheumatoid arthritis; RAS, Recurrent aphthous stomatitis; REEDA, Redness, edema, ecchymosis, discharge, approximation; REU, Reticular erosive ulcerative score; RF, Rheumatoid factor; rFLC, Free-light chain ratio; RISR, Radiation induced skin reactions; ROM, Range of motion; RORγ t, Retinoic-acid-receptor-related orphan nuclear receptor gamma; ROS, Reactive oxygen species; RT, radiotherapy; SBI, Sulcus bleeding index; SBP, Systolic blood pressure; SCCAI, Simple clinical colitis activity index; sCD40L, Cluster of differentiation 40 ligand; SGRQ, St. George respiratory questionnaire; SF-36, Short form healthy survey; SJC, Swelling joint count; SM, Sulfur-mustard; SMCs, Subjective memory complaints; SOD, Superoxide dismutase; SODA, Severity of dyspepsia assessment; SOFA, Sequential organ failure assessment; Sp, Substance P; SPEED, Standard patient evaluation of eye dryness; SRT, Selective reminding test; SSQOL, Stroke specific quality of life; sVCAM, Soluble vascular cell adhesion molecule; T2D, Type 2 diabetes mellitus; TAC, Total antioxidant capacity; TBARS, Thiobarbituric acid reactive substances; TBUT, Tear-film breakup time; TBX21, T-box transcription factor 21; TC, Total cholesterol; TEWL, Transepidermal water loss; Tf, *Tannerella forsythia*; TG, Triglyceride; TGF-β, Transforming growth factor-beta; TIBC, Total iron binding capacity; TJC, Tender joint count; TLC, Total lymphocyte count; TLR4, Toll-like receptor 4; TN, Total nitrite; TNF-α, Tumor necrosis factor alpha; TRP, Tryptophan; TRR, Transferrin receptor; TURB, Transurethral resection of bladder; TURP, Transurethral resection of prostate; UGT, Uridine diphosphate glucuronosyltransferase; uDPYD, Urinary deoxypyridinoline; UIBC, Unsaturated iron-binding capacity; VAS, Visual analog scale; VCAM, Vascular cell adhesion molecule; VEGF, Vascular endothelial growth factor; VO_2 max, Maximal oxygen consumption; WBC, White blood cells; WEC, Hot water extract; WPI; Whey protein isolate; WOMAC, Western Ontario and McMaster Universities osteoarthritis index; Zn, Zinc

(PANSS) and reduced Calgary depression scale for schizophrenia (CDSS) scores in schizophrenic patients with no reported adverse side effects compared to identical colored and sized placebo tablets.[86] Further, washing the mouth with curcumin and chitosan solution (10 mL) three times a day for 2 weeks inhibited *Candida* activity and achieved a complete response in 80% of denture stomatitis patients.[87] In another study mouthwash containing essential oils and curcumin (MEC) effectively reduced ESR, rheumatoid factor (RF), CRP, anticitrullinated peptide antibody (ACPA), plaque index (PI), pocket depth (PD), clinical attachment level (CAL) and also was found to be well-tolerated in rheumatoid arthritis (RA) patients with periodontitis.[88]

C3 complex/bioperine, a curcuminoid extract containing curcumin, desmethoxycurcumin, and bisdemethoxycurcumin in combination with bioperine (piperine), has been demonstrated to be anti-inflammatory, antidiabetic, and antiarthritic agent.[89−91] C3 complex/bioperine administered at the dose of 500 mg to 12 g per day for the duration of 7 days to months was safe, tolerated, and effective without any serious side effects.[40,89,90,92−104] Moreover, randomized clinical trials have shown that administration of C3 complex/bioperine (1 g/day of C3 complex plus 10 mg/day of bioperine) in patients with metabolic syndrome effectively reduced C-reactive protein (CRP), glucose, glycated hemoglobin (HbA1c), lipoprotein a (LPA), low-density lipoprotein cholesterol (LDL-C), nonhigh-density lipoprotein cholesterol (non-HDL-C), malondialdehyde (MDA), total cholesterol (TC), triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP), interleukin 6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), leptin, tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β), and upregulated adiponectin, HDL-C, and superoxide dismutase (SOD) levels compared to placebo containing the same amount of lactose and bioperine in a matched shape, size and color.[92−95] The treatment with this formulation was also shown to improve nonalcoholic fatty liver disease (NAFLD) by decreasing alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), hematocrit, erythrocyte sedimentation rate (ESR), iron, hemoglobin (Hb), LDL-C, TC, MCP-1, TNF-α, and epidermal growth factor (EGF).[96,97] Besides, C3 complex/bioperine formulation remarkably reduced TG, interleukin 1 beta (IL-1β), interleukin 4 (IL-4), PAB and vascular endothelial growth factor (VEGF), and enhanced zinc/copper (Zn/Cu) ratio in obese subjects.[98,105−107] In addition, in randomized double-blind clinical trials, oral intake of this formulation (1.5 g/day) for 6 weeks was shown to reduce MDA and oxidative stress levels and upregulated SOD and glutathione (GSH) levels in osteoarthritis patients.[91,108] Interestingly, in clinical trials administration of C3 complex (1−1.5 g/day) with bioperine (10−15 mg/day) for 4 weeks showed increased levels of glutathione peroxidase (GPx), SOD, catalase (CAT), and decreased levels of substance P (Sp), visual analog scale (VAS), pruritus severity, dermatology life quality index (DLQI) scores, interleukin 8 (IL-8), high sensitivity CRP (hs-CRP), calcitonin-gene related peptide (CGRP), FEV1, FVC, IL-6, TNF-α, TGF-β, MCP-1, St. George respiratory questionnaire (SGRQ) score and increased glutathione and COPD assessment test (CpAT) scores in patients with sulfur-mustard induced chronic pruritis and pulmonary complications.[89,99,109,110] Ingestion of this complex also showed antidiabetic effects by reducing glucose, C-peptide, HbA1c,

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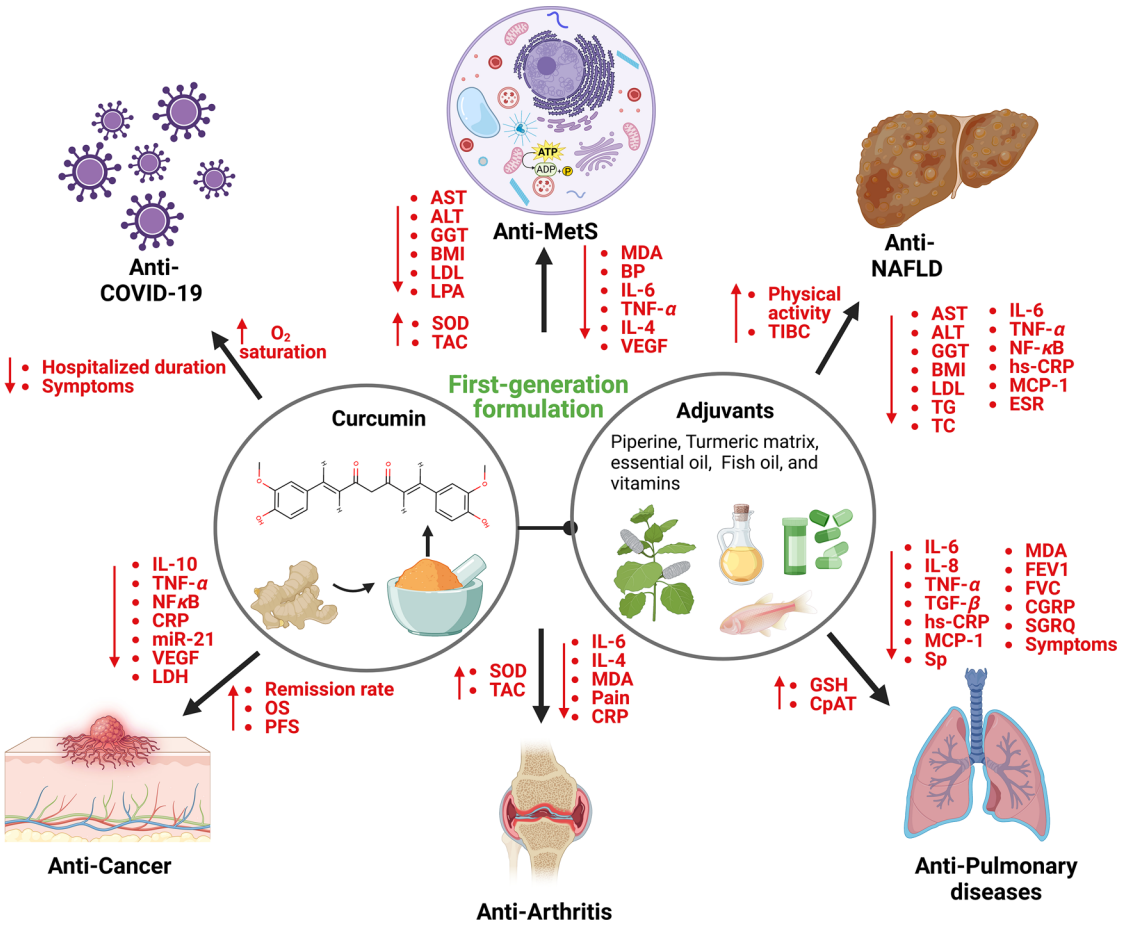

Figure 1. Broad range of biological activities and molecular mechanisms of first-generation curcumin formulations. The first-generation formulations have shown excellent enhancement in the absorption and cellular uptake of curcumin. Various phase I/II clinical trials demonstrated that these formulations are effective against arthritis, cancer, COVID-19, MetS, NAFLD, and pulmonary diseases by modulating inflammatory cytokines, oxidative stress-related molecules, liver enzymes, and lipid profiles. The figure was created using BioRender.com.

ALT, Non-HDL-C, LPA, MDA, and AST and increasing total antioxidant capacity (TAC) and SOD levels in diabetic patients.[90,104,111] Further, this regimen showed a promising effect in treating critically ill traumatic brain injury (TBI) patients by increasing GPx levels and suppressing leptin, IL-6, CRP, MCP-1, TNF-α, acute physiology, and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, and nutrition risk in critically ill (NUTRIC) score.[100,101] It was also shown to be effective in treating premenstrual syndrome (PMS) and dysmenorrhea with a remarkable reduction in AST, direct bilirubin, dysmenorrhea pain, and PMS screening tool (PSST) score and enhancement in vitamin D levels.[102,103] This C3 and piperine formulation, however, showed no significant effect on pro-oxidant antioxidant balance (PAB) in NAFLD patients after 8 weeks treatment.[112] Moreover, turmix tablet (300 mg curcumin plus 5 mg piperine) with or without turmix mouthwash for 12 weeks reduced burning sensation, improved mouth opening capacity, and tongue protruding ability in OSF patients.[113,114] However, this combination was shown to provide no effects on paracetamol metabolization in healthy subjects.[115]

BCM-95 is a novel well established curcumin formulation wherein curcumin is complexed with essential oils from turmeric rhizome, rice flour, vegetable cellulose, vegetable stearate, and silica.[116] BCM-95 has been shown to provide improved bioavailability and increased retention time of curcumin compared to curcumin-lecithin and curcumin-piperine formulations in healthy subjects.[117] Several clinical trials have proven the safety, tolerability, and efficacy of BCM-95 in humans.[117−121] BCM-95 is effective in treating multiple myeloma, multiple sclerosis, NAFLD, and prediabetic conditions by reducing BMI, weight, TC, TG, low-density lipoprotein (LDL), inflammatory molecules such as NF-κB, IL-6, TNF-α, and VEGF, liver enzymes including AST and ALT, diseases lesions, and hepatic fibrosis.[118−121] BCM-95 treatment increased high-density lipoprotein (HDL), overall remission rate, and physical activity in these patients.[118−121] In another study, oral intake of an active natural ingredient formulation (A total of 830 mg formulation consisting of fish oil 250 mg, phosphatidyl choline concentrated sunflower oil 150 mg, silymarin 75 mg, choline bitartrate 35 mg, curcumin 35 mg, D-α-tocopherol 10 mg) capsules (2 capsules/day) for 3 months was shown to be effective in decreasing liver enzymes such as AST, in patients with NAFLD compared to those who received tablet containing the same amount of choline and formulation excipients.[122] This shows that efficacy is attributed to curcumin but not to choline and hence, the anti-NAFLD effect is a stand-alone effect of administered first-generation curcumin formulation.[122] Although, ALT, and gamma-glutamyl transferase (GGT) levels were decreased in these patients after curcumin treatment the reduction was not found

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to be statistically significant. This formulation has also been shown to be safe and well-tolerated with no reported adverse side effects.[122] It was also shown that administration of another dietary supplement product CartiJoint Forte, a formulation of BCM-95, chondroitin sulfate, and glucosamine hydrochloride, resulted in a significant reduction in VAS score and WOMAC score in osteoarthritis patients with no noticeable adverse events compared to placebo group.[123] Another two novel BCM-95 formulations, CuraMed (552−578 mg of BCM-95 extracted in ethanol 99% (v/v) and 100% ethyl acetate, 49−52 mg volatile oil from *C. longa* containing 22−23.4 mg aromatic turmerone, and inactive excipients) and CuraMin (350 mg BCM-95, 150 mg of *Boswellia serrata* Roxb. ex Colebr gum resin extract corresponding to 75% boswellic acids and 10% 3-*O*-acetyl-11-keto-boswellic acid) have been demonstrated to ameliorate the pain, stiffness, degree of difficulty in moving the knee joint, and to enhance the physical performance in osteoarthritis patients. The placebo used in this study contained calcium phosphate, FD&C yellow 5, FD&C yellow 6, gelatin, magnesium stearate, maltodextrin, silica oxide, and titanium oxide. Both the formulations were found to be safe, well-tolerated, and did not show any serious adverse side effects on these patients.[124] Moreover, CuraMed also reduced postoperative discomfort and pain in periodontitis patients compared to control group who received mefenamic acid.[125] In another study, Curcugreen (dry turmeric rhizomes extracted with ethyl acetate called turmeric oleoresin, precipitated and combined with turmeric essential oil) alone or in combination with zinc was found to be effective in treating obesity by reducing body mass index (BMI), fasting plasma glucose (FPG), HbA1c, insulin, insulin resistance and increasing physical performance capacity compared to zinc with lactose as placebo tablets.[126] Besides, oral spray formulation of curcumin, ArtemiC containing 12 mg artemisinin, 40 mg curcumin, 30 mg frankincense, and 120 mg vitamin C in 1 mL spray when used twice a day for 2 days enhanced the clinical improvement, oxygen saturation and decreased fever and hospitalized duration in coronavirus disease 19 (COVID-19) patients compared to placebo spray (containing the same solvent of ArtemiC except for the active ingredients).[127] No reported adverse effects were observed in this trial.[127] Moreover, curcumin bioactive capsules containing 500 mg/day rutin, 1.5 g/day fish oil (18% EPA and 7% DHA), 50 mg/day curcumin (95% curcuminoids) along with 20 g whey protein isolate (WPI) for 12 weeks has been shown to ameliorate age-related sarcopenia as evidenced by enhanced gait speed and knee extension strength without any serious side effects.[128] In another study, CUC-1 formulation (curcumin with paclitaxel) administered intravenously (300 mg solution/week) increased physical performance and objective responsive rate (ORR) in metastatic breast cancer patients (MBC) (n = 150).[129] However, this intravenous infusion resulted in anemia and hematological grade 3−5 side effects in a few patients (n = 5).[129] Oral intake of two Coltect tablets (each tablet containing 500 mg curcumin, 250 mg green tea, and 100 μg selenium) per day for 8 weeks enhanced the remission rate and suppressed the clinical activity of ulcers in ulcerative colitis patients.[130] This formulation was also found to be safe and well-tolerated among these patients.[130]

Another formulation, Curcumall (curcumin C3 95%, turmeric, and ginger dissolved in glycerin and 0.4% alcohol) was shown to have no adverse effects on patients with oral lichen planus (OLP).[131] Additionally, curcumin dispersion amorphous formulation (500 mg/day) was reported to significantly reduce LDL-C, TG, AST, ALT, glucose, and HbA1c, and was safe, well-tolerated, and had no side effects in NAFLD patients.[132] Another study showed that curcumin capsules (Theravalues Co. Tokyo, Japan) containing 0.27% citric acid, 10% Curcumin, 2% other curcuminoids, 54.53% dextrin, 3.2% gum ghatti, and 30% maltose enhanced biological antioxidant potential (BAP), GSH and CAT and suppressed derivatives of reactive oxygen metabolites in healthy subjects with exercise-induced oxidative stress.[133] In addition, the novel curcumin formulation, Cureit/Acumin (46.5% total curcuminoids, 43% total carbohydrates, 5% fiber, 2.4% proteins, 3.2% volatile oil) exhibited enhanced bioavailability than phospholipid and volatile oil formulation of curcumin and was found to be safe without any side effects and improved handgrip strength, weight lifting capacity, walking distance and reduced the creatinine kinase (CK), muscle soreness and time taken to walk the same distance in healthy volunteers.[134−136] Another randomized study tested the effectiveness of curcumin essential oil formulation, curcumin phytosomal formulation, and γ-cyclodextrin curcumin formulation on healthy volunteers and reported enhanced curcumin absorption without adverse events.[137] Furthermore, curcuminoid turmeric matrix formulation (50% total curcuminoids, 3% essential oil, 2% protein, 40% total carbohydrate) suppressed CRP, rheumatoid factor (RF), SJC, TJC, ESR, and disease activity scores compared with food-grade starch as placebo in RA patients.[138] In another study, curcumin turmeric oil formulation (440 mg curcuminoid, 38 mg of turmeric oil) reduced mean weight, BMI, waist circumference, FBS, TG, hs-CRP, and increased adiponectin levels in T2D patients compared to administration of the same amount of rice flour as placebo.[139,140] Heng and colleagues showed that the application of curcumin alcohol gel reduced phosphorylase kinase activity, TRR, the severity of parakeratosis, and CD8+ T cells in psoriasis patients.[141] Similarly, the application of curcumin gel or curcumin mucoadhesive patch formulation reduced the burning sensation and improved mouth opening capacity in patients with OSF without any adverse side effects.[142,143]

Another novel curcumin formulation, Infla-Kine containing a proprietary blend of *Lactobacillus fermentum* extract, lipoic acid, burdock seed, papaya enzyme, zinc, and BCM-95 downregulated inflammatory cytokines such as IL-6, IL-8, NF-κB, and TNF-α thereby improved quality of life in healthy volunteers.[144] Iauril soft gels containing curcumin, quercetin, hyaluronic acid and chondroitin sulfate reduced dysmenorrhea, chronic pelvic pain, and dysuria in patients with endometriosis.[145] Killox, another curcumin formulation, (190 mg curcuminoids, 20 mg resveratrol, 100 mg NAC, 6 mg zinc with the formulation of enterosoma technology) reduced postoperative irritation duration and complications in patients who underwent transurethral resection of prostate, transurethral resection of bladder and with benign prostate hyperplasia (BPH).[146] The formulation did not induce any side effects and it was also found to be safe and well-tolerated in these patients.[146] In addition, LCD capsules (soft gel capsules containing lutein 20 mg, curcumin 200 mg, zeaxanthin 4 mg from marigold flower extract, algal source vitamin D3 600 IU, medium chain TG oil, linseed oil, olive oil, sunflower lecithin, tocopherol and thyme oil) improved Schirmer's strip wetness length, tear volume, TBUT score, SPEED score, OSDI score, corneal and conjunctival staining score, tear osmolarity, and MMP-9 positive score with comparative safety and no adverse

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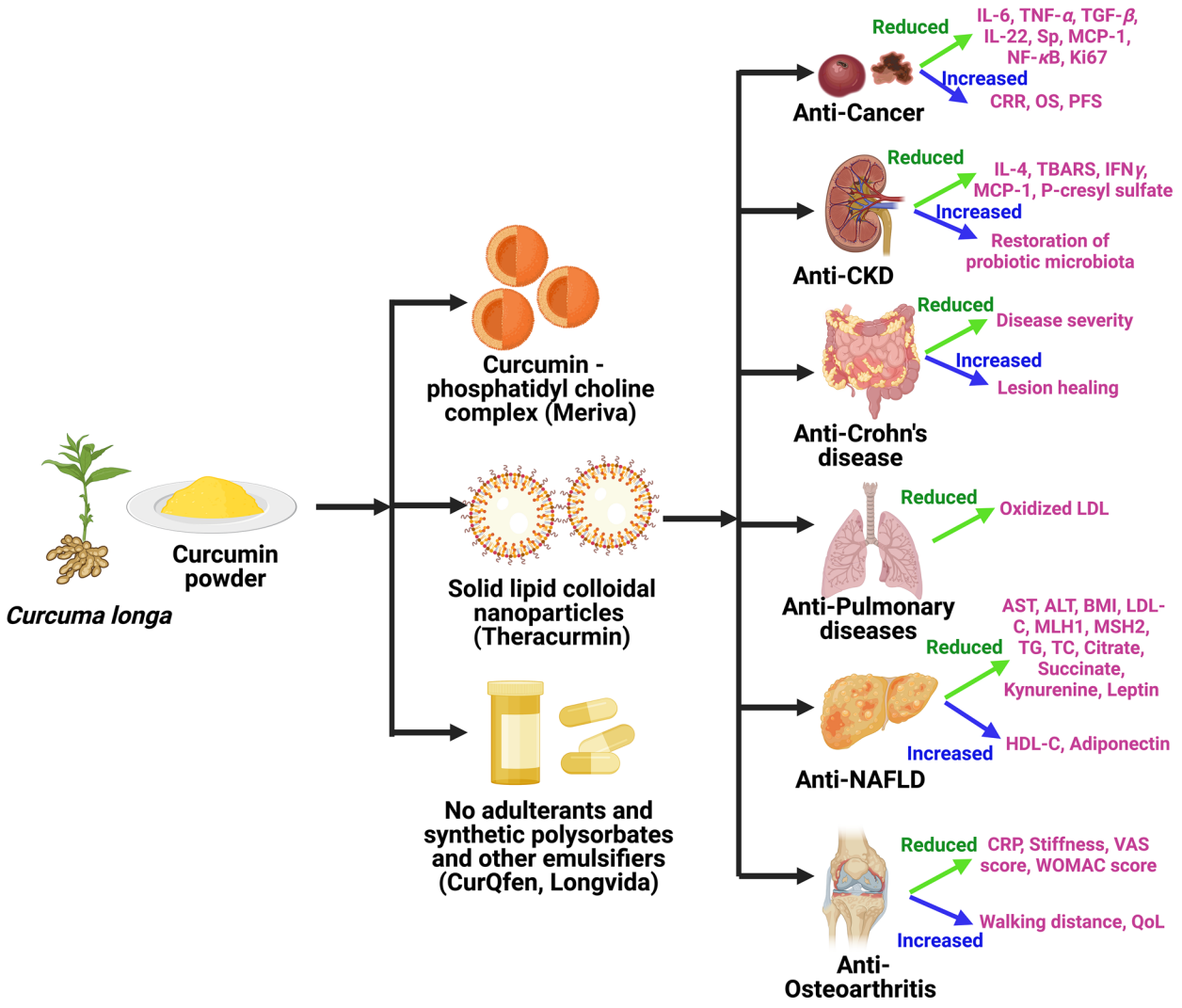

Figure 2. Novel next-generation formulations of curcumin and their biological effects. The promising next-generation formulations of curcumin including Meriva, Theracurmin, Longvida, and CurQfen have shown various clinical benefits including anticancer, anti-CKD, anti-Crohn's disease, anti-NAFLD, and antiosteoarthritis activities. The figure was generated using BioRender.com.

side effects in patients with dry eye syndrome in contrast to soyabean oil as placebo.[147] Moreover, natural product capsules manufactured by Vitacost consisting of 150 mg curcumin, 75 mg resveratrol, and 150 mg epigallocatechin-3-gallate for each 500 mg tablet was shown to reduce TNF-α induced NF-κB activation in healthy volunteers.[148] In another study administration of nutraceuticals with anti-inflammatory, oxidative, and nitrosative stress (NAIOS) containing L-carnitine, coenzyme Q10, curcumin, lipoic acid, quercetin or NAC, glutamine, taurine, and zinc reduced IgM mediated autoimmune responses, fibromyalgia, and fatigue rating and severity of diseases in patients suffering from myalgic encephalomyelitis/chronic fatigue syndrome.[149] Further, PureVida (460 mg of fish oil, 125 mg of Hytolive powder containing 12.5 mg of hydroxytyrosol, 50 mg of curcumin extract) formulation relieved pain and reduced CRP in breast cancer patients with no serious adverse side effects.[150] Another study showed that Reglicem formulation (chromium picolinate 100 μcg Cr, 200 mg curcumin dry extract, 200 mg berberine dry extract, 300 mg inositol, 40 mg banaba dry extract with 1% corosolic acid, silicon dioxide, magnesium stearate, dicalcium phosphate, microcrystalline cellulose) reduced FBS, postprandial blood sugar (PPBS), HbA1c, insulin, homeostatic model assessment (HOMA)-index, TG, TC, and CRP levels in fasting dysglycemia patients.[151] In another clinical trial, hot water extract of curcumin with or without pure curcumin powder for 8 weeks improved the water content of the skin and suppressed trans-epidermal water loss in healthy subjects.[152] Furthermore, Nutrafol women's capsule formulation (a proprietary blend of clinically tested and bio-optimized phytoactive extracts, vitamins, minerals, and botanicals including standardized extracts of ashwagandha, curcumin, piperine, capsaicin, hydrolyzed marine collagen, hyaluronic acid, organic kelp) augmented hair growth, quality, volume and thickness without any side effects in women with self-perceived hair thinning.[153]

Taken together, these results indicated that the first-generation curcumin formulations enhanced the absorption and bioavailability of pure curcumin and were effective against various ailments including autoimmune diseases, cancer, diabetes, hemoglobinopathies, oral diseases, and PMS.

4.2. Second-Generation Curcumin Formulation. Curcumin is readily soluble in fat. Hence, newer formulations have been developed to enhance the solubility of curcumin to

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enhance its absorption and bioavailability.[18,48] Over the years, various technologies have been utilized to enhance its solubility including the usage of polysorbates, phospholipid complexes, liquid droplet nanomicelle, and spray drying.[44] The novel curcumin second and third-generation formulations and their antichronic disease effects have been highlighted in Figure 2.

These second-generation formulations have shown excellent bioavailability and antiarthritic, anticancer, antidiabetic, and antiviral activities in numerous clinical trials (Table 2). For example, oral intake of 500 mg/day novel Actbiome formulation, (curcumin and asafetida complex was incorporated into turmeric fiber) for 8 weeks showed a reduction in IL-10 and gastrointestinal symptom rating scale (GSRS) score and increased fecal bifidobacteria, fecal lactobacilli, and ideal stool form and frequency without any side effects in healthy subjects.[154] Another study showed that a polysorbate formulation of curcumin named BioCurc/CLDM (85% curcumin, 13% desmethoxycurcumin, 2% bisdemethoxycurcumin, lauryl macrogol-32 glycerides, polysorbate-20, DL-alpha-tocopherol, hydroxy prolyl cellulose) (6 tablets, cross-over study) possess excellent absorption and bioavailability and safety in healthy individuals.[155] In addition, cyclodextrin formulation of curcumin known as Cavacurcumin along with omega-3 fatty acids (ω-3 FA), astaxanthin, gamma linoleic GLA, tocotrienols, hydroxy tyrosol, and vitamin D3 resulted in substantial reduction of hs-CRP, and SBP in healthy volunteers. This regimen was also well-tolerated without any adverse side effects.[156] Additionally, curcumin has also been formulated with hydrophilic carriers (CHC) to suppress its hydrophobicity and to enhance its solubility. The CHC formulation has been shown to increase curcumin bioavailability compared to standardized curcumin mixture, phytosomal curcumin formulation, and curcumin-turmeric volatile oil formulation in healthy volunteers.[157] This formulation has also been reported to be safe and did not cause any side effects in both healthy subjects and diabetic patients.[157,158] Besides, curcumin phosphatidylcholine along with irinotecan treatment has been shown to delay the disease progression without serious toxicity in patients with solid tumors.[41] Another phytosomal curcumin formulation, Curserin (200 mg curcumin, 480 mg phosphatidylcholine, 120 mg phosphatidylserine, and 8 mg piperine) increased HDL-C and decreased FPG, fasting plasma insulin (FPI), GGT, HOMA for insulin resistance (HOMA-IR), glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), lipid accumulation product (LAP), fatty liver index (FLI), TG, non-LDL-C, and hepatic steatosis index (HSI) in obese patients without adverse side effects.[159] In another study, oral intake of curcuminoid micelles capsules containing 20.1 mg curcumin, 3.9 mg demethoxycurcumin, and 0.5 mg bisdemethoxycurcumin was shown to be safe, well-tolerated, and enhanced the bioavailability of curcumin in healthy subjects.[160,161] Also, micellar curcumin formulation increased intratumor pH and inorganic phosphate levels in glioblastoma patients with minor side effects.[162] In another study, this formulation was shown to reduce creatinine kinase MB (CK-MB) in myocardial infarction patients.[163]

Another phospholipidic formulation FLAVOMEGA containing acetylcarnitine, acesulfame potassium, antiagglomerant, ascorbic acid, baicalin, coenzyme Q10, fructose, green tea catechins, phospholipidic curcumin, skullcap, and sucralose improved muscle strength, performance, and isokinetic knee extension and suppressed CK, reactive oxygen species, valine and free fatty acids in patients with Duchenne muscular dystrophy (DMD), facioscapulohumeral muscular dystrophy (FSHD), and limb-girdle muscular dystrophy (LGMD).[164] This formulation was also found to be safe, and well-tolerated without causing side effects.[164] Moreover, curcumin polysorbate formulation Flexofytol remarkably reduced Coll2-1, CRP, and global disease assessment activity in osteoarthritis patients in 3 months.[165] In another study, Flexofytol along with *Boswellia* extract pine bark extract, and methylsulfonyl methane for 12 weeks reduced activity impairment and FIHOA score without any significant adverse effects in osteoarthritis patients.[166] Another formulation HydroCurc consists of 80% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin entrapped in a LipiSperse delivery system, was demonstrated to inhibit the formation of thiobarbituric acid reactive substances (TBARS), TNF-α, IL-6, and relieved fatigue.[167] The formulation itself did not cause any side effects and further reduced the iron-induced gastrointestinal (GI) side effects.[167] Also, a single dose of HydroCurc along with maltodextrin enhanced IL-6, and IL-10, and reduced TC, pain, and capillary lactate dehydrogenase during the postexercise period in healthy young men.[168] In another study, Lipocurc formulation was shown to reduce PSA, CEA, and CA 19-9 in patients with advanced metastatic tumors without any side effects.[169] Although, lecithinized curcumin did not affect vitamin E in metabolic syndrome patients, reduced ratio of vitamin E/LDL, vitamin E/TC, and vitamin E/TG were noticed.[170]

As mentioned curcumin is least soluble in water with an estimated solubility of 11 ng/mL in alkaline conditions while it is readily soluble in lipids or fats.[43,171,172] Hence, efforts have been made to develop various lipid or phospholipid curcumin formulations and several of these formulations have shown tremendous potential as therapeutic agents.[173] For example, Meriva, a lecithin delivery method for curcumin, has better tissue dispersion and bioavailability than the unformulated natural substance.[64,173] This novel second-generation formulation has been shown to be safe and well-tolerated at a dose of 250 mg/day to 4 g/day for a period of 7 days to 8 months and did not cause any side effects both in healthy subjects and patients.[173−192] Moreover, this formation has been shown to ameliorate metabolic disorders including diabetes-associated edema and microangiopathy, hypercholesterolemia, metabolic syndrome, and NAFLD.[176,177,179−184,193−195] In various clinical trials, this formulation reduced skin flux, peripheral edema, retinal edema, LDL-C, TC, TG, LDL-C, non-HDL-C, uric acid, BMI, waist circumference, hip circumference, AST, ALT, portal vein diameter, liver size, 3-methyl-2-oxovaleric acid, 3-citrate, hippurate, hydroxyisobutyrate, indoxyl sulfate, α-ketoglutarate, kynurenine, methylamine, succinate, trimethylamine, chenodeoxy cholic acid, lithocholic acid, taurocholic acid, leptin, MutL homologue 1 (MLH1), and MutS homologue 2 (MSH2), and increased adiponectin levels, zinc levels, Zinc to copper ratio, PO_2, visual acuity, microcirculation score, in patients.[176,177,179−184,193,194] In another study, administration of Meriva (1 g/day) for 3 or 6 months caused a substantial reduction in MCP-1, IL-4, IFNγ, TBARS, *p*-cresyl sulfate, carbohydrate intake, protein intake, total fiber intake, phosphorus and potassium intake, and gut microbes such as *Escherichia-Shigella*, *Enterobacter verrucomicrobia*, Firmicutes, and improved other species of microbes including *Lactobacillaceae* spp., *Lachnoclostridium* spp., Lachnospiraceae family, and Prevotellaceae without side effects in patients suffering

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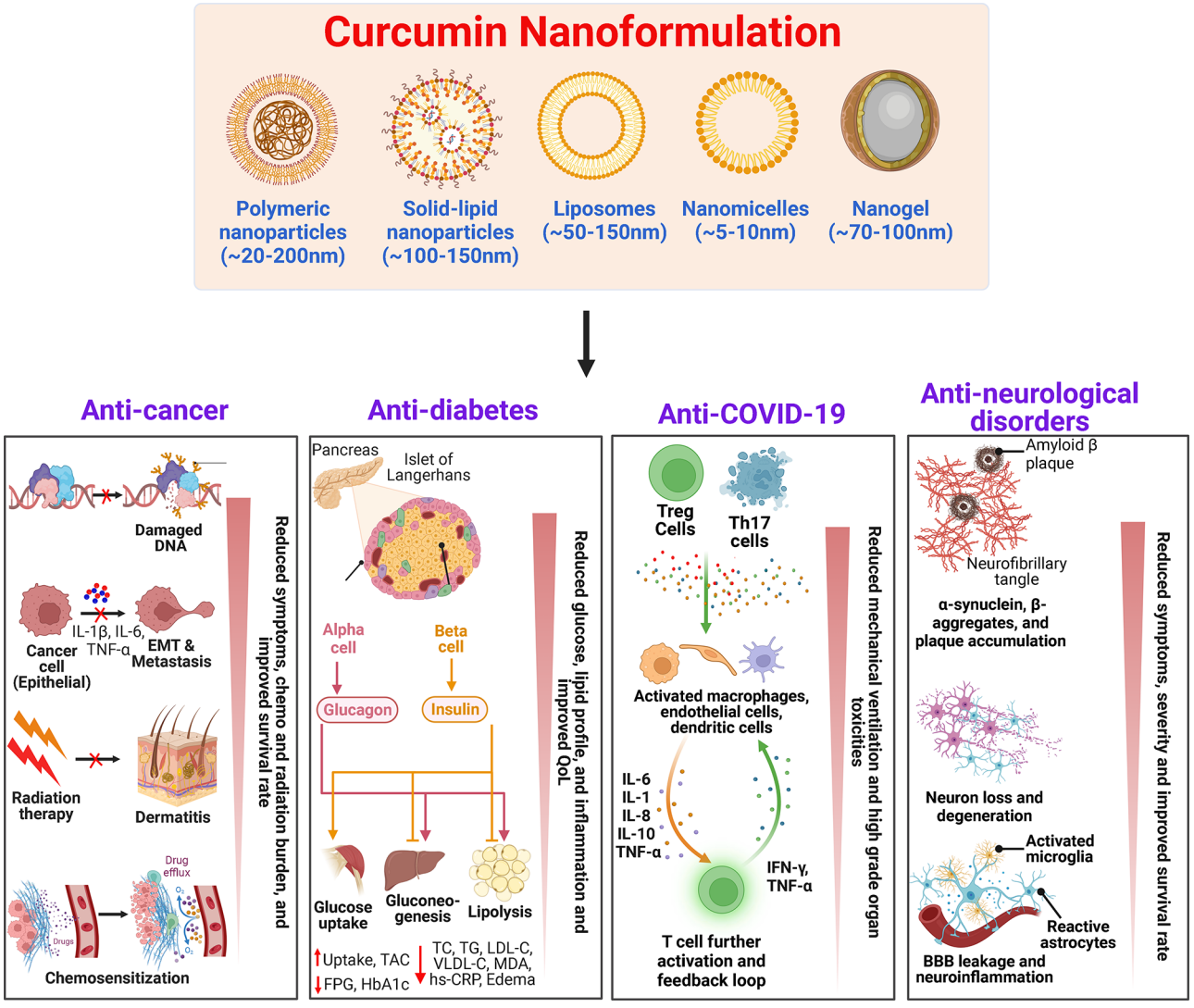

Figure 3. Molecular targets of curcumin nanoformulations. Increasing lines of evidence suggest that nanoformulations of curcumin possess high bioavailability and safety and are effective against various ailments. These formulations have been shown to inhibit DNA damage, inflammatory cytokines, lipid profile, and reduce amyloid plaque formation in the central nervous system. The figure was created using BioRender.com.

from chronic kidney diseases.[175] In addition, this formulation showed potential anticancer activities against solid tumors with enhanced safety, tolerability, and minimal adverse side effects.[187−189,191,192] It also improved response rate, stable disease period, inflammation, quality of life, and survival rate, and reduced the burden of chemotherapeutic side effects among these patients.[187−189,191,192] In addition, Meriva mitigated inflammatory markers such as CRP, IL-1β, IL-6, ESR, sCD40L, and sVCAM-1, WOMAC score, Karnofsky scale score, stiffness, negative effects on social function, and boosted physical performance capacity in osteoarthritis with excellent safety and tolerability (Figure 2).[185,186] It also reduced the risk of development of T2D and Alzheimer's disease in adults of age between 30 and 70 years.[190] Another study showed that this formulation (1 g or 4g/day) reduced the severity of gulf war illness disease without any serious side effects.[178] Moreover, Meriva along with fish oil reduced postprandial insulin levels in healthy subjects whereas Meriva with phytosterol reduced cardiovascular disease (CVD) risk in hypercholesterolemia patients.[179,196,197]

In another study, Meriva with anthocyanin has shown improvement in colorectal adenomatous polypos symptoms and it reduced NF-κB and Ki67 levels.[198] Further, another Meriva formulation called Algocur (each tablet contains 1g of Meriva) improved physical performance and reduced pain in men rugby players with osteo-muscular pain.[199] This formulation also showed to be safe and well-tolerated among these men.[199] Wolf and colleagues developed three different lipidated curcumin—NE65, NLC65, and NLC80—formulations reduced trans-epidermal water loss and modulated skin barrier functions in healthy subjects.[200] Another study showed that supplementation of Valdone curcumin soft gel (utilized self-emulsifying drug delivery system) improved clinical response and remission rates in ulcerative colitis patients.[201] Furthermore, topical application of curcuminoid-phosphatidyl choline formulated cream enhanced repigmentation in vitiligo patients.[202] However, another phytosomal curcumin formulation was shown to possess no considerable effect on aryl esterase activities in MetS patients.[203] Also, several studies have also revealed that phospholipidated formulations of both

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curcumin and curcuminoids were not considerably effective in treating patients with MetS.[204−208]

Nanoencapsulation or nanoformulation of curcumin is another promising strategy both to increase bioavailability and to decrease curcumin degradation rate in vivo.[23,43] Several synthetic and natural polymers, such as chitosan, *N*-isopropylacrylamide (NIPAAM), *N*-vinyl-2- polyethylene glycol monoacrylate (NIPAAM [VP/PEG A]), poly(lactic-*co*-glycolic acid), pyrrolidone, poly(vinyl alcohol) (PVA), and silk fibroin have been developed for curcumin nanoencapsulation.[43,209−212] Over the years, nanotechnology-based therapeutic delivery methods, including nanoparticles, liposomes, and nanoemulsions, have been developed.[213,214] The use of biochemical changes at the tissue microenvironment level in diseased states to initiate and activate drug release has replaced more traditional drug release mechanisms with the controlled-release mechanisms by novel engineered nanoparticle drug delivery systems.[214,215] Data indicated that these formulations increased treatment effectiveness while concurrently decreasing harmful side effects.[211,212,216,217] The novel nanocurcumin formulation developed by Exir Nano Sina (Iran) has shown excellent therapeutic efficacy in various diseases such as amyotrophic lateral sclerosis (ALS), ankylosing spondylitis (AS), arthritis, cancer, COVID-19, CVDs, diabetes, infertility, MetS, NAFLD, neurological and psychological disorders without side effects (Figure 3).[195,218−235] Administration of this formulation for 12 months increased the survival rate in ALS patients.[218] It also reduced RORγ t, IL-17, IL-23, miR-141, miR-155, miR-200, and symptoms in AS patients.[219] The antiarthritic potential of this formulation has been evidenced by its capacity in suppressing CRP, $CD4^+$ and $CD8\ T^+$ cells, Th 17 cells, B cells, miRNA-155, miRNA-138, miRNA-16 and VAS score, and augmenting Treg cells without any adverse events in the clinical trials involving osteoarthritis and RA patients.[225,226,236] It was also shown to be effective in treating Behcet's disease where it improved Treg cells, FOXP3, TGF-β, IL-10, miRNA-25, and miRNA-106b.[237]

Multiple clinical trials have shown its potential in treating COVID-19 disease with admirable safety and tolerability. Nanocurcumin formulation in COVID-19 patients led to reduced levels of GM-CSF, IFNγ, IL-1β, IL-6, IL-17, IL-18, IL-21, IL-23, RORγ t, T-box transcription factor 21 (TBX21), and TNF-α, and induced FOXP3, IL-4, IL-10, IL-35, and TGF-β levels.[238−242] It also improved lymphocyte count, oxygen saturation levels, symptoms, and Treg cell frequency and reduced symptom resolution time, hospitalized duration, and mortality rate in COVID-19 patients.[221,222,238−243] Several studies have also revealed the beneficial effects of nanocurcumin formulation in treating critically ill patients with sepsis. Nanocurcumin from Exir-Nano-Sina (Iran) suppressed Bcl-2, inflammatory molecules such as ICAM-1, IL-1β, IL-6, IL-18, TLR-4, TNF-α, and VCAM-1, creatinine, lipid profile, liver enzymes and reduced mechanical ventilation period in these patients.[227,244,245] In addition, nanocurcumin treatment enhanced clinical response rate and ameliorated radiation-induced dermatitis in various cancers including bladder, head and neck, and prostate cancers.[224,246,247] It also reduced DNA damage and micronuclei formation in lymphocytes of thyroid cancer patients.[228] Moreover, the antidiabetic properties of nanocurcumin were attributed their capacity in reducing FBG, glycated Hb, insulin, hs-CRP, TC, TAC, TN, LDL-C, VLDL-C, TC/HDL-C, MDA, and augmented insulin sensitivity, TAC, peroxisome proliferator-activated receptor gamma (PPARγ), LDLR, and GSH levels in T2D patients.[248−251] It also suppressed neuropathy, depression, and anxiety in T2D-associated peripheral neuropathy patients.[251,252] Nanocurcumin supplementation for 10 weeks improved sperm count, sperm motility, and testosterone levels in patients with infertility complaints.[229] This study also showed that nanocurcumin increased testosterone levels and reduced follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin levels, although not statistically significant.[229] This formulation has also been shown to decrease TG, HOMA-β, and MDA, and upregulate adiponectin levels and TAC in MetS patients.[230,253] Further, treatment with this formulation remarkably reduced the degree of fatty liver, liver enzymes, lipid profile, and inflammatory mediators in patients with NAFLD.[254] This formulation was also effective in treating neurological disorders such as migraine, multiple sclerosis, and Parkinson's disease and was able to improve disease severity, symptoms, and deregulated miRNAs with no or mild GI side effects.[231,232,255−260] It also reduced pain, severity, lesion area, and burning sensation in patients with various oral diseases including gingivitis, mucositis, and OLP.[247,261−264] In another study, this formulation enhanced the responsive rate while reducing the positive and negative PANSS subscale score in schizophrenia patients.[233] Further, nanocurcumin formulation from Theravalues Corp., Japan was demonstrated to down-regulate IL-6, hs-CRP, MDA, and upregulate IL-10, brain-derived neurotrophic factor (BDNF), and TAC in MetS patients.[265] Furthermore, several other nanocurcumin formulations have also been developed by various laboratories and these formulations have shown tremendous potential in helping healthy subjects and treating various chronic diseases such as arthritis, cancer, NAFLD, neurological disorders, oral diseases, and skin diseases.[266−279] Thus, nanocurcumin formulation with enhanced bioavailability and safety has been promising in treating several human diseases.

A distinctive example of a submicron crystal dispersion of curcumin known as Theracurmin was reported to have 27-fold higher bioavailability in comparison with pure curcumin.[49] Increasing lines of evidence also suggested its enhanced bioavailability with acceptable safety and mild side effects in healthy subjects and cancer patients (Figure 2).[116,280−286] It has also been shown to reduce exercise-induced muscle soreness and increased the range of motion.[287,288] In postmenopausal women, it reduced brachial SBP.[289] This formulation also improved clinical response rate and lesion healing and reduced endoscopic disease severity in Crohn's disease patients.[290] In another study, Theracurmin significantly reduced mRNA expression of IL-6 in PBMCs and serum levels of IL-6 in hemodialysis patients.[291] Another salient example of clinical benefits of Theracurmin comes from the trial on osteochondral diseases in which it reduced roughness in the femur bone and stiffness in the knee joint.[292] It also inhibited the raise in oxidized LDL in both COPD and T2D patients.[293,294]

Collectively, these studies suggest that second-generation formulations of curcumin improved the bioavailability of curcumin and their significance drives the ancillary goal to develop them as therapeutic drugs.

4.3. Third-Generation Curcumin Formulation. An expansive frontier in nutraceuticals is unfolding third-generation curcumin formulation via increasing the bioavailability of "free" curcuminoids without using synthetic polysorbates and/or emulsifiers.[44,295] These formulations are

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well established to have superior absorption, BBB-permeability, cellular uptake, and better tissue distribution.[295,296] Based on the published literature, these formulations have greater than 100-fold higher bioavailability compared to pure curcumin.[47] Besides, these formulations are devoid of adulterants and contaminants, making them safer and nongenotoxic and nonhepatotoxic for long-time clinical use.[44] Indeed, third-generation formulations have been developed recently and these formulations include curcumin galactomannan formulation or CurQfen (noncovalent complex between curcumin and fenugreek galactomannans), curcuRouge (Starch and curcumin formulation), Curcuwin Ultra (cellulosic derivatives and curcumin formulation), and Longvida (soy lecithin and curcumin formulation) (Figure 2).[47,295,297] CurQfen was shown to be safe and well-tolerated and had no adverse side effects have been reported in clinical trials.[44,298−301] This formulation also improved α- and β-waves of EEG, memory improvement, and reduced choice-based-visual reaction time in healthy subjects.[302] It also improved walking performance, VAS score, and WOMAC score, and inhibited the rise in hs-CRP, IL-1β, and IL-6 levels in osteoarthritis patients.[298,301] In addition, its antiobesity and anti-CVD properties were attributed to its increased levels of HDL and reduced levels of homocysteine within 12 weeks of treatment.[300] Besides, to a certain extent, this formulation relieved occupational stress as evidenced by improvement in QoL, SOD, GPx, GSH, and fatigue.[299] In another study, curcuRouge was demonstrated to reduce the neutrophil to lymphocyte ratio without any safety issues in healthy subjects.[303] Another formulation Curcuwin Ultra+ showed enhanced bioavailability and was found to be safe in healthy subjects.[304] Another next-generation formulation with superior bioavailability, Longvida was also elucidated to reduce fatigue, and oxidative stress, tension, and anxiety, and improved mood-related issues, and cognitive functions in healthy individuals with excellent safety and no side effects.[305−308] Moreover, clinical trials on obese patients have revealed that Longvida intake improved cerebral artery stiffness, cerebrovascular responsiveness, and lipid profile without side effects.[309−311] It has also been shown to be beneficial in treating both OSF and osteoarthritis.[312,313] Another illuminating clinical trial evidenced the use of Longvida in detecting amyloid spots in the retina of Alzheimer's patients and reported that this formulation exhibits a greater capacity to identify these spots in positron emission tomography (PET) scanning compared to conventional amyloid PET in longitudinal evaluation of amyloid risk and neurodegeneration (LEARN) study.[314]

Certainly, these clues warrant further investigations on third-generation curcumin formulations as a novel nutraceutical formulation in diagnosing and treating various ailments.

5. CONCLUSION

Advances in chemistry and technologies have provided the versatility and tools to develop a range of innovative curcumin formulations with considerable improvement in oral bioavailability and safety. Decades of research on curcumin and its formulations resulted in the increased oral bioavailability of curcumin from 11 ng/mL to 626.98 μg/mL. These curcumin formulations were found to be safe and well-tolerated even at higher doses ranging from 2 g/day to 12 g/day and for a prolonged duration of 6 months to an year. The simplest first-generation formulation with adjuvants to second-generation with polysorbates to third-generation with only natural material have shown tremendous absorption capacity, cellular uptake, and safety not only in diseased but also in healthy subjects providing the evidence of disease prevention and treatment capability of these formulations. As we noted at this time, few of these regimens including curcumin plus piperine combination, BCM-95, nanocurcumin, Meriva, and Theracurmin have been tested clinically and are effective against chronic diseases such as arthritis, autoimmune diseases, cancer, diabetes, endometriosis, hemoglobinopathies, metabolic syndrome, neurological disorders, obesity, oral diseases, psychological disorders, and skin diseases. All the formulations have been shown beneficial effects compared to either placebo such as calcium phosphate, lactose, rice flour, and starch, or the standard care treatment. Major grade 3 side effects, GI intolerability, and hepatotoxicity were reported when curcumin was administered intravenously earlier. Nevertheless, the minor side effects in most of these trials with oral intake of curcumin formulations include cold, irritation, indigestibility, and nausea which in few cases might be attributed to adjuvants and emulsifiers. However, clinical studies are scarce at this time on upcoming and more promising third-generation formulations. Notably, it is advisable to opt for highly bioavailable curcumin formulations that have demonstrated their therapeutic efficacy at a relatively low dosage of 80−500 mg/day. Further, most of the clinical trials conducted were restricted to a small number of patient groups. However, more research is needed to examine the safety and effectiveness of curcumin formulations in both large and diverse patient populations with different phases of the disease. As such, all these formulations cannot be inherently compared due to dissimilarities in the dose, duration of treatment, clinical study design, formulation type, the method used for analysis, and population disparity. Recently, as detailed earlier, curcumin formulation was also used to diagnose the amyloid spots clinically. Therefore, curcumin formulations have significant potential to serve as preventive, diagnostic, and therapeutic entities.

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Author Contributions

M.H. contributed to the initial drafting of the manuscript, review of literature, table preparation, visualization, and overall editing; S.G. contributed to the initial drafting of the manuscript and overall editing; B.B. and R.V. provided critical overall manuscript editing and revision; A.B.K. contributed to conceptualization, funding, overall supervision, and supported review development and overall editing.

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Notes

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