Curcumin-piperine co-supplementation and human health: a comprehensive review of preclinical and clinical studies

Abstract

Curcumin is extracted from the rhizomes Curcuma longa L. It is known for its anti-inflammatory and anti-oxidant activities. Despite its safety and potential for use against various diseases, curcumin's utility is restricted due to its low oral bioavailability. Co-administration of curcumin along with piperine could potentially improve the bioavailability of curcumin. The present review aimed to provide an overview of the efficacy and safety of curcumin-piperine co-supplementation in human health. The findings of this comprehensive review show the beneficial effects of curcumin-piperine in improving glycemic indices, lipid profile and antioxidant status in diabetes, improving the inflammatory status caused by obesity and metabolic syndrome, reducing oxidative stress and depression in chronic stress and neurological disorders, also improving chronic respiratory diseases, asthma and COVID-19. Further high-quality clinical trial studies are needed to firmly establish the clinical efficacy of the curcumin-piperine supplement.

Keywords: curcumin, piperine, health, clinical, preclinical

Introduction

Curcumin is a member of the Zingiberaceae family (Kuttan, Bhanumathy, Nirmala, & George, 1985). The largest producer of curcumin worldwide is India, which is used as a home remedy for several conditions (Esatbeyoglu et al., 2012). In addition, Curcumin is widely used for various ailments in traditional Indian and Chinese medicine (Kuttan et al., 1985). For example, curcumin preparations are applied to wounds. It has also been used in some hepatobiliary conditions and as an anthelminthic agent (Nelson et al., 2017). Curcuminoid showed a group of compounds such as curcumin, bis-demethoxycurcumin, demethoxycurcumin and cyclic curcumin obtained from turmeric. Of these compounds, curcumin and cyclic curcumin are the major and minor components, respectively (Priyadarsini, 2014). Curcumin is a bioactive polyphenolic pigment, which is chemically known as [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] (Abdollahi, Momtazi, Johnston, & Sahebkar, 2018; Castro Frabel do Nascimento et al., 2012). Curcumin has been approved as a safe agent by various world health authorities, including the US Food and Drug Administration (Alikiaii, Bagherniya, Askari, Sathyapalan, & Sahebkar, 2021).

A very recent systematic review indicated the beneficial effects of curcumin on various conditions, including renal and prostate diseases, oral and dental diseases, osteoarthritis, rheumatoid arthritis, neurological diseases, gastrointestinal diseases, psychological conditions, epilepsy and non-alcoholic fatty liver diseases (NAFLD) (Atefi et al., 2021; Mohammad Bagherniya et al., 2021; M. Bagherniya, M. Darand, et al., 2021; M. Bagherniya, D. Soleimani, et al., 2021; Bishnoi, Chopra, Rongzhu, & Kulkarni, 2011; Ehteshami et al., 2021; Fakheran et al., 2021; Gharibpour et al., 2021; Mohammad Jalali et al., 2020; Mohseni et al., 2021; Shirban et al., 2021; Shokri-Mashhadi, Bagherniya, Askari, Sathyapalan, & Sahebkar, 2021; Xu et al., 2018). In addition, Curcumin has various antioxidant and anti-inflammatory activities, which

play a substantial role in the beneficial effects observed in clinical studies. Apart from these activities, curcumin also has immunomodulatory, analgesic, anti-microbial, anti-rheumatic, anti-cancer and hypouricemic activity (figure 1) (Alikiaii, Bagherniya, Askari, Johnston, & Sahebkar, 2021; Kotha & Luthria, 2019; Saberi-Karimian et al., 2020; White & Lee, 2019; Z. J. Yang et al., 2022).

Despite the pronounced health benefits reported from curcumin, in new studies, mainly curcumin-piperine has replaced the use of curcumin alone in investigating the effect of this phytochemical on various diseases. To the best author's knowledge, to date, there is no study to summarize the efficacy of curcumin-piperine based on clinical trials. The present review aimed to provide an overview of the efficacy and safety of curcumin-piperine co-supplementation in human health. This comprehensive review discusses the employability of curcumin-piperine as a nutraceutical in the prevention, treatment, and management of prevalent human diseases and associated conditions.

Methods

In this narrative review, Scopus, PubMed, Web of Science, and Google Scholar were searched using the following key terms in titles and abstracts: ("curcumin" OR "curcuma" OR "curcuminoid" OR "curcuma longa" OR "curcumin-piperine" OR "curcumin-bioperine"). Medical subject headings (MeSH) were used to identify qualified articles. English articles (both preclinical and clinical studies) published from inception to January 2022 were included.

The mechanism of curcumin in human health

The versatile properties of curcumin are due to its ability to interact with a broad range of molecular targets (Panahi, Khalili, Hosseini, Abbasinazari, & Sahebkar, 2014). It is a scavenger of reactive oxygen species (Hatcher, Planalp, Cho, Torti, & Torti, 2008; Maheshwari, Singh,

Gaddipati, & Srimal, 2006). Also, curcumin modulates the expression of genes involved in lipoprotein metabolism (Panahi et al., 2014). Moreover, studies have shown the anti-inflammatory effects of curcumin are mediated through the down-regulation of inflammatory cytokines, transcription factors and pro-inflammatory enzymes (Aggarwal & Sung, 2009; Mollazadeh et al., 2019). It is proposed that curcumin inhibits certain transcription factors, including NF-kB and activating protein-1 (AP-1), thereby blocking cytokine gene expression. Also, the down-regulation of intercellular signaling proteins, such as protein kinase C, is a potential mechanism. Curcumin also inhibits the phosphorylation of inhibitory factor I-kappa B kinase, which suppresses NF-kB activation (Jurenka, 2009). In addition, curcumin decreases lipoxygenase (LOX) production, which increases leukotriene 4 (LTE-4) levels. The activation of NF-Kb increases inflammatory cytokines such as TNF-α. Curcumin suppresses NF-Kb activation, thereby decreasing the production of acute-phase proteins such as serum amyloid A, C reactive protein (CRP), α1-antichymotrypsin and fibrinogen in the liver (Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017; Karczewski et al., 2018; Tanaka, Narazaki, & Kishimoto, 2014). NF-Kb also increases the level of nitric oxide (NO) through increasing inducible NO synthase (iNOS) production, which affects vascular endothelial growth factor (VEGF). NF-Kb also increases the level of COX-2 and, thus, prostaglandin E2 (PGE2). PGE2 and LTE-4 are both metabolites of polyunsaturated fatty acids, which play an important role in enhancing inflammation. Curcumin reduces inflammatory markers by acting on several pathways (Figure 2).

Limitation of curcumin in clinical trials

Despite its safety and potential for use against various pathological states, curcumin's utility is limited because of its low oral bioavailability (Kunnumakkara et al., 2019). For example, after intravenous injection, the maximum serum concentration of 0.360.05g/mL was obtained, while

a maximum plasma concentration was only 0.06 ± 0.01 μg/mL after oral administration. This suggests that the oral bioavailability of curcumin is just 1% (K.-Y. Yang, Lin, Tseng, Wang, & Tsai, 2007). Similarly, after intraperitoneal administration of 0.1 g/kg curcumin to mice, a plasma curcumin level of 2.25 μg / ml was reached. In comparison, after oral administration (1.0 g / kg), the peak plasma level was only 0.22 μg / ml (Pan, Huang, & Lin, 1999). So far, studies on the pharmacokinetics of curcumin have revealed poor absorption, a high rate of metabolism, and rapid systemic elimination, which severely reduces its bioavailability. Furthermore, curcumin is poorly water-soluble (Zhang et al., 2012) and is prone to degradation, especially in alkaline conditions. At pH>7, curcumin degrades in 30 min. However, curcumin degradation is much slower under acidic conditions, with less than 20% of total curcumin degraded in an hour (Marczylo, Steward, & Gescher, 2009; Tønnesen & Karlsen, 1985). In addition, most of the absorbed oral curcumin is rapidly processed in the liver and plasma (Hoehle, Pfeiffer, Sólyom, & Metzler, 2006), transformed into water-soluble metabolites and excreted through urine, resulting in low levels of free circulating curcumin (Holder, Plummer, & Ryan, 1978; Ireson et al., 2001). Furthermore, a large part of the oral curcumin is excreted in a non-metabolized form (Ammon & Wahl, 1991). Nevertheless, despite its low bioavailability, curcumin has been found to improve human metabolism. Hence, current approaches to utilising curcumin as a therapeutic strategy include combining curcumin with other substances or developing curcumin formulations with enhanced bioavailability (Dulbecco & Savarino, 2013).

Curcumin-piperine

Piperine [1-[5-[1,3-benzodioxol-5-yl]-1-oxo-2,4, pentadienyl] piperidine] is an alkaloid extracted from Piperaceae seeds (Lai et al., 2012; Meghwal & Goswami, 2013). It is known as black pepper and is used as a food spice (Ahmad et al., 2012). Piperine has attracted attention as a spice with antioxidant and anti-inflammatory activities. The molecule also exerts

antihypertensive, antitumor, anti-asthmatic, analgesic, and other health benefits (Smilkov et al., 2019). It is known to lower serum lipids (Srinivasan, 2007). Piperine has also been shown to facilitate the digestive process via stimulating various intestinal and pancreatic enzymes (Ahmad et al., 2012). Piperine has been used in traditional and modern medicines to alleviate several health conditions (Meghwal & Goswami, 2013). Piperine potentially enhances the bioavailability of several nutrients and pharmacological agents by promoting absorption through various mechanisms (Haq et al., 2021). Piperine improves the diffusion of drugs into the blood vessels located in the intestine wall (Atal, Dubey, & Singh, 1985). Piperine has been shown to inactivate cytochrome P450 (CYP) 3A (CYP3A), which has a crucial role in drug metabolism (Cui et al., 2020). Furthermore, when combined with resveratrol, it improves anti-inflammatory properties (Pannu & Bhatnagar, 2019). Piperine also moderates the membrane dynamics and enhances the permeability of the absorption site. In addition, piperine increases the serum half-life of coenzyme Q10 and beta-carotene, improving their efficacy and contact time. However, it lowers the metabolism of different drugs by inhibiting various metabolizing enzymes (Haq et al., 2021). As a result, the co-administration of curcumin and piperine appears to be a practical strategy for increasing the bioavailability of curcumin. Serum levels of curcumin were either undetectable or very low when given a dose of 2 g curcumin alone, while coadministration of piperine increased the bioavailability by up to 2000% (Shoba et al., 1998). Combining curcumin with piperine could improve curcumin bioavailability by inhibiting the activity of curcumin metabolizing enzymes through inhibiting glucuronidase in both the intestine and liver and reducing liver conjugation of curcumin with glucuronic acid and its elimination via urine (Figure 3).

Experimental studies on curcumin-piperine

In several experimental studies, the effect of curcumin with piperine in comparison with curcumin alone and the control group on various metabolic and neurological diseases has been investigated, which is described below and summarized in Table 1:

In 2 studies, Kaur et al. demonstrated antihyperglycemic, hypolipidemic and antioxidant benefits and effects on body weight of the combination of curcumin with piperine and quercetin (CPQ) for 28 days on streptozotocin-induced diabetic rats which reveals that CPQ may be beneficial in patients with type 2 diabetes mellitus.

In one study, male Sprague-Dawley rats (n=30) were fed on a high-fat diet (HFD) for eight weeks. After developing hyperlipidemia (HLP), except for rats in the HFD control group, rats received curcumin, piperine, or curcumin + piperine for four weeks. Co-administration of curcumin plus piperine strengthened the hypocholesterolemic effects of curcumin by increasing the activity of cholesterol 7α-hydroxylase (CYP7A1), lecithin cholesterol acyltransferase (LCAT), apolipoprotein AI (ApoAI), and low-density lipoprotein receptor (LDLR). This study provided evidence for the enhanced efficacy of this combination for the treatment of HLP (Tu et al., 2014). In a study by Miyazawa et al., HFD-induced obese mice were divided into five groups to continue on a high-fat diet or receive a calorie restriction (CR) (reduce 10% HFD intake for ten weeks, 20% for 20 weeks) with curcumin, piperine, curcumin + piperine or none of these for 20 weeks. The results indicated that supplementing the CR diet with curcumin + piperine significantly increased body fat loss and suppressed HFD-induced inflammation compared to ad libitum-fed animals. While supplementing CR diets with curcumin or piperine alone did not increase further reduction in body fat (Miyazawa et al., 2018). However, in another study on obese mice with a similar design to Miyazawa et al., in all CR mice, regardless of curcumin or piperine supplementation, metabolic and immune/inflammatory profiles improved significantly (Wang et al., 2013).

FindingFindingsn experimental study indicated that the administration of piperine or curcumin, less their combination, to Wistar rats with N-nitro-L-arginine-methyl ester-induced hypertension led to a reduction in blood pressure. In addition, the spices improved the remodeling of the aortic wall induced by hypertension. However, their combination had similar effects on blood vessel morphology as curcumin alone (Hlavačková et al., 2011).

In an animal study, male Wistar rats were treated with piperine, curcumin, or curcumin+ piperine for 49 days orally, initiated a week before D-galactose was administered intraperitoneally for the induction of aging. This study suggested that curcumin plus piperine exerted a better response in improving cognition and prevention of senescence compared to monotherapy. In addition, the results showed improved spatial memory and signaling, reduced oxidative burden and accumulation of lipofuscin, and increased hippocampal volume (Banji, Banji, Dasaroju, & Annamalai, 2013). Also, in another study by Banji et al., treated young Wistar rats with D-galactose were simultaneously treated with piperine or curcumin or curcumin+ piperine for 56 days. They demonstrated significant improvement in memory and sensorimotor performance with curcumin and piperine treatment. As a result, the combination of these antioxidants may minimize the risk of neurodegenerative disorders

In one study, forty-eight male Swiss albino mice were treated with curcumin, piperine, or curcumin+ piperine for seven days, followed by lipopolysaccharide (LPS) administration. Pretreatment with curcumin+ piperine prevented LPS-induced anhedonic, depressive-like behaviors, oxido-nitrosative stress, and the attenuation effect on pro-inflammatory cytokines in the hippocampus region compared to LPS treated group and curcumin treatment groups alone. Thus, piperine enhanced the neuroprotective effect of curcumin against LPS-induced defects (Jangra et al., 2016). Also, co-administration of curcumin and piperine had a beneficial effect against Quinolinic acid (QA)-induced neuronal abnormalities. QA-induced motor deficit,

behavioral abnormalities, and biochemical and neurochemical abnormalities were studied in adult Wistar rats receiving QA for 21 days compared to treatment with curcumin alone and the control group (Singh & Kumar, 2016). Administration of curcumin prevented all the behavioral and neurochemical changes induced by haloperidol-associated neurotoxicity in male Wistar rats compared with the control group. Co-administration of piperine significantly enhanced the effects of 25 mg/kg of curcumin but not of curcumin 50 mg/kg.

The findings of Rinwa et al. supported the protective effects of curcumin plus piperine against chronic unpredictable stress (CUS)-induced cognitive impairment and oxidative damage. There was a reduction in locomotor activity, decreasing levels of malondialdehyde (MDA), nitrite concentration, and the levels of antioxidative enzymes were restored along with lowering acetylcholinesterase and serum corticosterone levels in male Laca mice under a battery of stressors for 28 days compared to treatment with curcumin alone and control (CUS) group (Rinwa & Kumar, 2012). Another study on rats with olfactory bulbectomy (OBX) induced depression showed that curcumin plus piperine significantly potentiated neuroprotective effects against OBX-induced depression via modulating oxidative-nitrosative stress-induced stress neuroinflammation and apoptosis as compared to curcumin alone (Rinwa, Kumar, & Garg, 2013). Based on another experimental study, curcumin plus piperine prevented behavioral, neurochemical and neuroinflammatory changes. In addition, it preserved the antioxidant potential of the nigro striatum in 6-hydroxydopamine-induced parkinsonian rats.

In several experimental studies, the effect of one-week uses of a combination of curcumin plus piperine on various disorders of male Swiss albino mice receiving benzo(a)pyrene (BaP) (125mg/kg). They observed that pretreatments of curcumin+ piperine before administration of BaP reduced DNA damage by decreasing 8-oxo-dG content and % DNA in the comet tail, and moderated toxicity and redox imbalance by reducing the levels of lipid peroxides (LPO),

thiobarbituric acid reactive substances (TBARS), protein carbonyl content (PCC), and increasing the level of GSH and enzyme activities of glutathione peroxidase (GPx), glutathione reductase (GR), SOD, CAT, and glutathione-S-transferase (GST) in lungs and liver of mice compared to treatment with curcumin alone and control group (Sehgal, Kumar, Jain, & Dhawan, 2012a, 2012b). Also, pretreatments with curcumin plus piperine significantly decreased the activities of ethoxy resorufin o-demethylase (EROD), pentoxyresorufin o-dependentylase and the level of benzo(a)pyrene-diol, (BaP) epoxide DNA adducts with consequent increment in quinone reductase activities compared to treatment with curcumin alone and control group (Sehgal, Kumar, Jain, & Dhawan, 2013). In another study, Balb/c mice were sensitized on days 0, 7, and 14 and challenged from days 16–30 on alternate days with a 200 µl solution of ovalbumin. Mice were pretreated with curcumin and piperine alone and in combination via intraperitoneally on days 16–30 and compared with intranasal curcumin treatment. Finally, the total number of inflammatory cells was reduced in all treated groups, but no significant difference in curcumin + piperine was observed compared to other groups. At the same time, intranasal curcumin has shown a maximum reduction in inflammatory cells suggesting therapeutic potential in allergic asthma.

According to the findings of Balakrishnan et al., administration of curcumin + piperine (five days) has a potent antigenotoxic effect via suppression of the formation of TBARS and normalization of the function of antioxidant enzymes during 7,12 dimethyl benz[a]anthracene (DMBA)-induced genotoxicity in golden Syrian hamsters (Balakrishnan, Vellaichamy, Menon, & Manoharan, 2008). Shi et al. showed that the corn-soybean basal diet supplemented with curcumin + piperine and a high dose of curcumin could improve the performance and intestinal barrier function and suppress oxidative stress of Wuzhishan piglets (Shi et al., 2020).

Clinical trial studies on curcumin-piperine

The effect of the co-administration of curcumin and piperine on different diseases has been compared with the control group in various clinical trial studies, as described below. The findings of the articles are summarized in Table 2:

Nonalcoholic Fatty Liver Disease (NAFLD)

Daily supplementation of piperine and curcuminoids for 12 weeks in patients with NAFLD significantly improved NAFLD severity. However, no effect was observed on serum levels of liver enzymes, lipid profile, glycemic index and iron (Panahi et al., 2019). Also, in the study of Mirhafez et al., supplementation with the same dose for eight weeks did not show a significant change in serum pro-oxidant and antioxidant balance (as an indicator of oxidative stress) in these patients (Mirhafez et al., 2019). However, administration of 500 mg/day curcumin plus 5 mg/day piperine (8 weeks), in addition to significant improvement in body weight and NAFLD severity, improved serum levels of alkaline phosphatase and inflammatory cytokines compared with the placebo group in NAFLD patients (Mirhafez et al., 2021; Saberi-Karimian et al., 2020). Clinical trials in this field are scarce, although based on available trials, it seems that curcumin-piperine might be a new therapeutic agent against NAFLD; more well-designed RCTs are required in this area.

Type 2 diabetes mellitus

In three studies, Panahi and colleagues evaluated the effect of daily supplementation with 1000 mg curcuminoids plus 10 mg piperine in patients with T2DM. The findings of the studies indicated a significant reduction in total cholesterol (TC), non-high-density lipoprotein-cholesterol (non-HDL-c) and lipoprotein (a) (Lp(a)) and an increase in HDL-c, but triglyceride (TG) and LDL-c did not significantly change after 12 weeks in the intervention group compared to the placebo group. Supplementation for twelve weeks significantly increased adiponectin and decreased the leptin: adiponectin ratio and leptin levels, which is reflected by a reduction in TNF-

α (Panahi, Khalili, Sahebi, Namazi, Atkin, et al., 2017). After eight weeks of receiving the same dose, serum TAC and SOD activity increased dramatically, whereas serum MDA levels decreased significantly (Panahi, Khalili, Sahebi, Namazi, Karimian, et al., 2017). Another study found that 500 mg curcuminoids + 5 mg piperine supplementation for 12 weeks improved glycemic and hepatic markers but not hs-CRP in T2DM patients (Panahi et al., 2018). In addition, Neta et al. discovered that taking 500 mg curcumin + 5 mg piperine for 120 days reduced hyperglycemia and TG levels in T2DM. In summary, curcumin-piperine showed promising effects regarding inflammatory, stress oxidative and some of the lipid parameters in patients with T2DM.

Metabolic syndrome

The results of 4 studies support a significant improvement in serum concentrations of lipid profile (Panahi et al., 2014), adipokines (Yunes Panahi, Mahboobeh Sadat Hosseini, Nahid Khalili, Effat Naimi, Sara Saffar Soflaei, et al., 2016), oxidative (SOD, MDA) and inflammatory status (Yunes Panahi et al., 2015; Yunes Panahi, Mahboobeh Sadat Hosseini, Nahid Khalili, Effat Naimi, Luis E Simental-Mendía, et al., 2016) after administration of 1000 mg curcuminoids plus 10 mg piperine for eight weeks in patients with metabolic syndrome. Though generally, more studies are needed to show curcumin piperine's efficacy on these subjects. Nevertheless, as well as its efficacy on T2DM, this phytochemical might have favorable effects on inflammatory, oxidative stress and some of the lipid parameters of patients with metabolic syndrome.

Obesity

According to Mohajer et al., four weeks of supplementation with the piperine-curcuminoid combination significantly increased the zinc/ copper (Zn/Cu) ratio. At the same time, no significant alteration was observed in serum concentrations of Zn, Cu and SOD activities (Mohajer et al., 2014). Furthermore, Moohebati et al. found no differences in small dense low-

density lipoprotein (sdLDL) in obese dyslipidemic patients (Moohebati et al., 2014). However, a very small number of studies in this field make it impossible to get a definitive conclusion.

Traumatic brain injury

Two studies examined the effect of one-week uses of a combination of curcumin and piperine on critically ill patients with traumatic brain injury (TBI) (Shadnoush et al., 2020; Zahedi et al., 2021). Shadnoush et al. observed that supplementation with curcumin + piperine significantly reduced leptin but had no significant effect on serum adiponectin concentrations compared with placebo. On the other hand, Zahedi et al. found that curcuminoid supplementation had a beneficial effect on inflammatory markers and clinical outcomes of TBI patients (Zahedi et al., 2021). Although it seems that curcumin-piperine might have beneficial effects on patients with traumatic brain injury, a very small number of studies in this field make it impossible to get a definitive conclusion.

COVID-19 and other respiratory diseases

Oral administration of 525 mg curcumin with 2.5 mg piperine twice a day for two weeks as symptomatic adjuvant therapy in COVID-19 treatment could lead to significantly improved symptoms, less deterioration, better ability to maintain oxygen saturation above 94% on room air, and clinical outcomes compared to controls. Also, it could significantly reduce morbidity, mortality, and duration of hospitalization in patients with moderate/severe symptoms (Pawar et al., 2021). Another study showed that curcumin-piperine co-supplementation with 500 mg curcumin and 5 mg piperine twice a day for two weeks in outpatients with COVID-19 could significantly improve weakness (Askari et al., 2022). Furthermore, the positive effects of adjunctive therapy with a combination of piperine and curcumin on systemic oxidative stress and St. George Respiratory Questionnaire (SGRQ) scores (as an indicator of the severity and frequency of respiratory symptoms and health-related quality of life (HRQoL)) were observed in

subjects with Chronic Pulmonary Complications due to sulfur mustard exposure. Considering the antimicrobial and antiviral effects of curcumin and with regard to the available trials, it seems that curcumin-piperine may be useful in treating OCVID-19 as an adjunct therapy.

Other diseases

The findings of Mahato et al. support a significant improvement in posttreatment reduction in visual Analog Scale (VAS) score for burning sensation and an increase in mouth opening (MO), mucosal flexibility (MF), and tongue protrusion (TP). In addition, there was a significant increase in the epithelial thickness and a decrease in collagen deposition in patients with oral submucous fibrosis receiving curcumin (500 mg), piperine (5 mg), and lycopene (25 mg) twice a day for 12 weeks. Kaul et al. conducted a three-week trial in individuals with moderate gingivitis to assess the effects of systemically delivered 300 mg curcumin, 5 mg piperine, and 10 mg lycopene together with scaling and root planing (SRP). When antioxidants were administered systemically as an addition to SRP, the results showed that they could produce greater inflammation resolution (S. Kaur, Sharma, Sarangal, Kaur, & Prashar, 2017).

The study by Panahi et al. aimed to investigate the efficacy of the combination of curcumin and piperine as an additive to standard antidepressants in major depressive disorder. There was a significant alleviation of anxiety and depression symptoms compared to standard antidepressive therapy alone. In another study, daily administration of curcumin, piperine, and taurine for three months significantly decreased serum IL-10 and miR-21. This way, it may improve the overall survival rate in patients with hepatocellular carcinoma. Delecroix et al. found that taking 6g of curcumin and 60mg of piperine every day between 48 hours before and 48 hours after exercise can attenuate some aspects of exercise-induced muscle damage (Delecroix, Abd Elbasset Abaïdia, Dawson, & Dupont, 2017). In a pilot study, the gut microbiota profiles of healthy

humans were examined from three groups: placebo, turmeric, and curcumin treatment for eight weeks. The microbiota of participants showed significant heterogeneity over time and individualized response to therapy. Curcumin and turmeric affected the gut microbiota in the same way among the responsive participants, implying that curcumin may be responsible for the changes in turmeric-treated participants (Volak et al., 2013). Khonche et al. showed that the addition of 500 mg curcuminoids + 5 mg piperine to the standard triple treatment to eliminate H.pylori in patients with peptic ulcers improved symptoms safely and relieved in some cases dyspepsia but had no significant effect on the eradication of H. pylori infection (Khonche et al., 2016).

Discussion

The results presented in this comprehensive review of experimental and clinical studies suggest the beneficial effects of co-administration of curcumin and piperine in improving glycemic indices, lipid profile and antioxidant status in diabetes and improving the inflammatory and stress oxidative status caused by obesity and metabolic syndrome. In addition, this supplement reduces oxidative stress and depression in chronic stress and neurological disorders. The most exciting evidence of the combination is improving respiratory symptoms and complications in chronic respiratory diseases, asthma and COVID-19. The curcumin-piperine administration as an adjunctive therapy can play a multifaceted role in treating COVID-19 and significantly reduce its complications and mortality. While numerous clinical trials are underway to assess the therapeutic effects of this supplement in various diseases (Table 3), clinical evaluation in neurological disorders is limiting. Also, the evidence of the effectiveness of this supplement is limited in certain conditions (Table 1, 2).

Based on our best findings, there has been no other comprehensive review or systematic review and meta-analysis on the health-promoting effects of curcumin-piperine specifically, which would be possible to compare the findings of the present study. Still, our findings are consistent with the results of meta-analyses on the effect of curcumin supplementation in various diseases.

Similar to our findings, a recent meta-analysis of 16 RCTs showed that curcumin supplementation had beneficial effects on NAFLD severity and BMI in patients with NAFLD (Ngu, Norhayati, Rosnani, & Zulkifli, 2022). However, the results of meta-analyses on the effect of curcumin supplementation on liver enzymes in these patients are different (Goodarzi, Sabzian, Shishehbor, & Mansoori, 2019; M. Jalali et al., 2020; Ngu et al., 2022; Wei et al., 2019). Curcumin suppresses NF-kB and leads to the reduction of oxidative stress and inflammation, making it an antioxidant and anti-inflammatory agent (Jovičić, Jozinović, Grčević, Spaseska Aleksovska, & Šubarić, 2017). This finding enhances the probability that curcumin can aid liver protection by reducing oxidative stress, as oxidative stress is involved in NAFLD pathogenesis (Sumida, Niki, Naito, & Yoshikawa, 2013). In addition, Curcumin decreases BMI via inhibiting differentiation of adipocyte tissue by increasing adenosine monophosphate-activated protein kinase and suppressing peroxisome proliferator-activated receptor γ (PPAR- γ), resulting in enhanced lipolysis (Bradford, 2013).

In line with our review, two separate meta-analyses on 7 RCTs have confirmed the beneficial effects of curcumin on some lipid parameters in patients with diabetes and metabolic syndrome (Altobelli et al., 2021; Azhdari, Karandish, & Mansoori, 2019). A meta-analysis by Ferguson et al. on 28 RCTs provided evidence for the anti-inflammatory efficacies of curcumin through a notable reduction in CRP, IL-6, IL-8, and TNF-α (Ferguson, Abbott, & Garg, 2021). The antioxidant and anti-inflammatory properties of curcumin were also confirmed in another meta-analysis on 15 RCTs by a remarkable improvement in MDA, hs-CRP, and IL-6 (Tabrizi et al.,

2019). The functional mechanism by which curcumin demonstrates its lipid-lowering properties appears to be an interaction with the expression of several genes, including PPAR-α, lipoprotein lipase, and cholesterol ester transfer protein (Qin et al., 2017). Curcumin can improve plasma plasma levels of TG and cholesterol by inhibiting the expression of lipogenic genes (Farzaei et al., 2018).

As mentioned, studies investigating the effect of curcumin and its derivatives on neurological disorders are limited. Still, the public mechanism of curcumin treatment action in this field includes brain monoamine oxidase (MAO)-A or B activity blockage, serotonin receptor modulation, improvement of serotonin, dopamine, and brain noradrenaline levels, increasing neurotrophic factor and neuronal growth, promoting neuroprotection, as well as, reducing oxidative stress, neuroinflammation, and apoptosis (Choi et al., 2017; Patel et al., 2020). In addition, the molecular mechanism of curcumin's antidepressant and anti-anxiety effects include increasing brain-derived neurotrophic factor (BDNF), 5-hydroxytryptamine (5-HT), and noradrenaline, and decreasing acetylcholinesterase (AChE) activity, TNF-α and IL-6 levels, NF-kB activation, and plasma corticosterone levels (Bahramsoltani, Rahimi, & Farzaei, 2017) (Farzaei et al., 2016).

Vahidian-Azimi et al. found in a meta-analysis of 6 RCTs that adjunctive treatment with diverse formulations of curcumin reduced common symptoms, length of hospitalization and mortality in COVID-19 patients with various levels of disease severity (Vahedian-Azimi et al., 2022), which is similar to the present review findings. Curcumin has an inhibitory efficacy versus the human respiratory syncytial virus (RSV) infection by inhibiting RSV replication, TNF-α release, and downregulating phospho- NF-kB (Obata et al., 2013). In fact, curcumin modulates intercellular signaling pathways essential for impressive virus replication, such as weakening NF-kB and PI3K/Akt signaling (Zahedipour et al., 2020). Curcumin also has anti-inflammatory and anti-

fibrotic efficacy by attenuating the expression of important cytokines and chemokines associated with a lung infection, such as IL-6, IL-10, IFNγ, and MCP-1 (Avasarala et al., 2013).

To our knowledge, the present review was the first comprehensive review that evaluated the efficacy of curcumin and piperine co-administration on human health. However, several limitations of this study should be mentioned. First, most of the results involved a small number of participants and a limited number of studies. Second, most of the studies lasted 12 weeks or less; thus, it is not probable to present the long-term efficacies of curcumin-piperine supplementation on various diseases and aspects of health. Third, different doses of this supplement were used in the evaluated studies. Fourth, a comparatively high number of studies have been conducted in Iran.

Conclusion and future perspectives

Based on the current evidence from this comprehensive review, co-administration of curcumin and piperine is a promising, novel, practical approach without any major side effects in managing various metabolic, inflammatory, and respiratory diseases. At the same time, clinical evaluation in neurological disorders is limited. Therefore, it is suggested that future research should focus more on evaluating the effectiveness of this combination on mood and neurological disorders. In addition, further high-quality clinical trial studies are needed to establish the curcumin-piperine supplement's clinical efficacy.

Figure legends

Figure 1. Schematic pathways of the beneficial effects of curcumin and its potential mechanism pathways.

Figure 2. The schematic pathways of the effectiveness of curcumin of inflammatory markers, potentially reducing the inflammation in the human body. Several mechanisms have been suggested demonstrating the inhibitory effects of curcumin on inflammation. It inhibits the regulation of specific transcription factors, thereby blocking the expression of cytokine gene expression. Another potential mechanism is the down-regulation of intercellular signaling proteins, such as protein kinase C. Curcumin also blocks the phosphorylation of inhibitory factor I-kappa B kinase, suppressing the activation of NF-kB. Curcumin decreases LOX production. LOX increases the levels of LTE-4. Curcumin suppresses NF-Kb activation; on the other hand, NF-Kb activation results in increased inflammatory cytokines, increasing the production of acute-phase protein. NF-Kb also increases the level of NO through increasing iNOS production. NO increases VEGF. NF-Kb also increases the level of COX-2. COX-2 increases the level of PGE2. LTE-4 and PGE2 are both metabolites of polyunsaturated fatty acids, which play a key role in increasing inflammation. These pathways indicate that curcumin, through several mechanisms, reduces inflammatory markers.

CRP, C reactive protein; AP-1, activating protein-1; LT, leukotriene; PG, prostaglandin; LOX, lipoxygenase; COX, cyclooxygenase, iNOS, inducible NO synthase; NO, nitric oxide; TNF-α, tumor necrosis factor-α; VEGF; Vascular endothelial growth factor; NF-Kb, nuclear factor-KB;

Figure 3. Chemical structure of curcumin and piperine

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Table 1. Summarize of the experimental studies

Author, Year, Country	Disease	Agent/ Dose per day	Treatment duration	Animals	Main outcome
Kaur, 2012, India (G. Kaur & C, 2012)	HFD & Low-Dose Streptozotocin-induced diabetes	100 mg/kg curcumin or (curcumin + piperine + quercetin - 100 mg/kg) or (curcumin + piperine + quercetin - 50 mg/kg)	28 days	Albino female wistar rats received HFD and STZ (30 mg/kg)	• Treatment with CPQ significantly reduced plasma level of glucose, TG, LDL, and TC and also significantly increased the downregulated plasma HDL and glucose tolerance vs. control HFD and low-dose STZ fed rats. • The decreased levels of antioxidant enzymes (CAT, GSH, and SOD) was increased by the administration of CPQ.
Kaur, 2016, India (G. Kaur, Invally, & Chintamaneni, 2016)	Streptozotocin and nicotinamide-induced diabetes	100 mg/kg curcumin or (curcumin + piperine +quercetin - 100 mg/kg)	28 days	Swiss albino mice and Wistar rats received STZ and nicotinamide	• Significant decrease in the raised LDL, TG, TC, plasma glucose in the CPQ fed group vs. diabetic control as well and curcumin only group. • Improvement in body weight and glucose tolerance with CPQ vs. diabetes control and curcumin only group.
Tu, 2014, China (Tu et	HFD induced Hyperlipidemia	curcumin or piperine or curcumin + piperine	4 weeks	male Sprague-Dawley rats with HFD	• Co-administration of Cur + reduced TC, TG and LDL in the serum & liver, increase in HDL and fecal TG, TC, and total bile acid, vs. administration of Cur alone. • Cur plus Pip - significant upregulation of ApoAI, LCAT, CYP7A1 and LDLR vs. administration of Cur alone.

al., 2014)					
Miyazawa, 2018, USA (Miyazawa et al., 2018)	caloric restriction in HFD-induced obesity	Curcumin or piperine or Curcumin + piperine	20 weeks	male C57BL/6 mice underwent CR (reduced 10% HFD intake for 10 weeks, 20% for 20 weeks)	• Supplementing CR diet of obese mice with Cur + Pip significantly reduced AUC of percent total body fat and IL-1β and KC/GRO vs. ad libitum fed animals.
Wang, 2013, USA (Wang et al., 2013)	caloric restriction in HFD-induced obesity	Curcumin or piperine or Curcumin + piperine	5 weeks	male C57BL/6 mice underwent CR)	• Compared to HFD controls, CR mice, regardless of Cur and/or Pip, had lower body weight, fat mass, lower blood glucose & insulin. They had lower IL-1β, TNF-α, PGE2. • Mice with CR alone had higher splenocyte proliferation and IL-2 production, which was reduced by Cur and/or Pip supplementation.
Hlavačková, 2011, Slovakia (Hlavačková et al., 2011)	L-NAME induced hypertension	piperine or curcumin alone or combination of piperine and curcumin	6 weeks	Wistar rats treated with L-NAME	• The combination of curcumin with piperine decreased the blood pressure.
Banji, 2013, India	D-galactose induced senescence	piperine or curcumin alone or combination	49 days	Young adult male Wistar rats treated with D-galactose	• Significant reduction in MDA with the Cur + Pip in vs. the D-Gal alone.

(Banji, Banji, Dasaroju, & Annamalai, 2013)		of piperine and curcumin			• Increase in GSH, SOD and CAT with Cur + Pip vs. the control group and monotherapy with Cur or Pip. • Finding superior response with Cur + Pip in comparison to monotherapy by improving spatial memory, hippocampal volume and signaling, reducing oxidative load and lipofuscin accumulation, and protecting hippocampal neurons.
Banji, 2013, India (Banji, Banji, Dasaroju, & Kranthi, 2013)	lipid and protein oxidation induced by D-galactose	curcumin (20 mg/kg) or piperine (7.5 mg/kg) or piperine (7.5 mg/kg)+ Cur (20 mg/kg) or piperine (15 mg/kg) + Cur (40 mg/kg)	56 days	Young Wistar rats treated with D-galactose	• Significant improvement in sensorimotor performance, memory, reduced oxidative and nitrosative burden with combination treatment. • Minimal changes in Purkinje cells in treatment with curcumin + piperine
Jangra, 2016, India (Jangra et al., 2016)	Lipopolysaccharide-Induced neurochemical and neurobehavioral Deficits	curcumin or piperine or curcumin + piperine	7 days	male Swiss albino mice treated with LPS	• Pretreatment with Cur in combination with the piperine significantly prevented the LPS-induced anhedonic and depressive-Like behaviors vs. LPS treated group and curcumin treatment groups alone. • Coadministration of curcumin with piperine showed protection against LPS-induced oxido-nitrosative stress and significantly potentiated the attenuation effect on pro-inflammatory cytokines in the hippocampus

Singh, 2016, India (Singh & Kumar, 2016)	Quinolinic Acid Induced Neurodegeneration	Curcumin (25 and 50 mg/kg/ day, p.o.) or combination of Curcumin (25 mg/kg/day, p.o.) with piperine (2.5 mg/kg/day, p.o.)	21 days	adult Wistar rats received QA	• Co-administration of Pip with Cur compared to treatment with Cur alone and control group showed: • Improvement in the body weight • Reduction in behavioral abnormalitties, oxido-nitrosative stress and inflammatory cytokines • Significantly preventation the increase in DOPAC and • HVA levels in striatum and fluctuation in levels of adenosine, GABA, glutamate
Bishnoi, 2011, India (Bishnoi et al., 2011)	Haloperidol-Associated Neurotoxicity	Curcumin (25, 50 mg/kg,) **or** Piperine (2.5 mg/kg) **or** Curcumin (25, 50 mg/kg,) **and** piperine (2.5 mg/kg)	21 days	Male Wistar rats treated with Haloperidol	• Administration of Cur prevented the behavioral and neurochemical changes in comparison with control group • Co-administration of Pip significantly enhanced the effect of 25 mg/kg but not with 50 mg/kg of curcumin.
Rinwa, 2012, India (Rinwa & Kumar, 2012)	Chronic unpredictable stress - induced cognitive impairment & oxidative stress	curcumin (100, 200, and 400 mg/kg, p.o.) or piperine (20 mg/kg, p.o.) or curcumin (100, 200, mg/kg, p.o.) + piperine (20 mg/kg, p.o.)	28 days	Male Laca mice	• Co-administration of Cur with Pip significantly attenuated locomotor activity, levels of oxidative stress markers, mitochondrial enzyme complex activities, as well as lowered acetylcholinesterase and serum cortisol levels compared to other groups.
Rinwa, 2013,	Olfactory bulbectomy induced depression	curcumin or piperine or curcumin + piperine	2 weeks	Adult male Wistar rats	• Co-administration of Pip + Cur significantly potentiated neuroprotective effects against OBX induced depression as compared to Cur alone.

India (Rinwa et al., 2013)					
Singh, 2017, India (Singh & Kumar, 2017)	6-hydroxydopamine-induced Parkinsonian rats	curcumin (25 and 50 mg/kg) or piperine (2.5 mg/kg) + curcumin (25 mg/kg)	21 days	Hemi-Parkinson's rat intranigral infusion of 6-OHDA	• Concomitant administration of Cur and Pip compared to treatment with Cur alone and control group showed: • Significantly ameliorated the loss in body weight, oxidative stress and the increase in DOPAC and HVA • Increase 5-HIAA levels in striatum • Significantly attenuated the impaired grip strength, locomotor activity and the GABA degeneration
Sehgal, 2011, India (Sehgal, Kumar, Jain, & Dhawan, 2011)	benzo(a)pyrene induced DNA damage	curcumin (100mg/kg) or piperine (20mg/kg) or curcumin (100mg/kg) + piperine (20mg/kg)	One week	male Swiss albino mice received BaP	• Pretreatments of Cur+ Pip before administration of BaP decreased DNA damage in liver and lungs compared to treatment with Cur alone and control group
Sehgal, 2012, India (Sehgal et al., 2012b)	benzo(a)pyrene induced redox imbalance	curcumin (100mg/kg) or piperine (20mg/kg) or curcumin + piperine	One week	male Swiss albino mice received BaP	• Pretreatments with Cur plus Pip decreased the levels of LPO, TBARS, PCC, and with consequent increase in the levels of tissue antioxidants compared to treatment with Cur alone and control group. Pretreatment with Cur increased the GST activity in BaP treated group, which was enhanced further by combination treatment with Pip+ Cur.

Sehgal, 2012, India (Sehgal et al., 2012a)	benzo(a)pyrene - mediated toxicity	curcumin (100mg/kg) or piperine (20mg/kg) or curcumin (100mg/kg) + piperine (20mg/kg)	One week	male Swiss albino mice received BaP	• Pretreatments with Cur plus Pip significantly reduced LPO, PCC, and incidence of MNPCEs but elevated the level of GSH and enzyme activities compared to treatment with Cur alone and control group.
Sehgal, 2013, India (Sehgal et al., 2013)	-	curcumin (100mg/kg) or piperine (20mg/kg) or curcumin (100mg/kg) + piperine (20mg/kg)	One week	male Swiss albino mice received BaP	• Pretreatments with Cur plus reduced EROD, PROD, and BaPDE-DNA adducts with consequent increment in QR activities compared to treatment with Cur alone and control group.
Chauhan, 2018, India (Chauhan, Jaiswal, Subhashini, & Singh, 2018)	Ovalbumin-Induced Chronic Asthma	curcumin (10,20 mg/kg b.w, i.p.) or piperine (5 mg/kg b.w, i.p.) or curcumin (10, 20 mg/kg b.w, i.p.) + piperine (5 mg/kg b.w, i.p.) or curcumin (5 mg/ kg, bw, i.n.)	14 days	Balb/c mice sensitized with OVA with alum	• Inflammatory cells were reduced in all treated groups • significant reductions were not seen in Cur +Pip. While, intranasal Cur has showed maximum inflammatory cells reduction • The cur (i.n.) group showed maximum reduction in ROS level
Balakrishnan, 2008,	DMBA-Induced Genotoxicity	curcumin (80 mg/kg b.w) or piperine (50	5 days	golden Syrian hamsters injected with DMBA	• Significant reduction in frequency of MnPCEs and % of chromosomal aberrations in the bone marrow of hamsters receiving Cur+ Pip compared to either agent alone.

India (Balakrishnan et al., 2008)		mg/kg b.w) or curcumin + piperine			• Cur+ Pip have a potent antigenotoxic effect via suppression the formation of TBARS and normalization antioxidant enzymes
Shi, 2020, China (Shi et al., 2020)	-	piperine or curcumin (200 mg/kg as low-Cur) or curcumin (300 mg/kg as high-Cur) or curcumin (200mg/kg) + piperine (50 mg/kg)	21 days	Wuzhishan piglets weaned	• The F/G and plasma d-lactate and DAO of the Cur + Pip and high-CUR groups were less than in control group, while occludin, claudin-1, and zonula occluden-1 in jejunal and ileal mucosa were significantly higher in the Cur + Pip and high-Cur groups than in the control group. • The piglets in the Cur + Pip and high-Cur groups had higher serum and intestinal mucosa activity of SOD and GPx and significantly lower MDA than piglets in the control group.

Cur: curcumin; Pip: piperine; MnPCEs: micronucleated polychromatic erythrocytes; s.c.: subcutaneous; i.p.: intraperitoneal; i.n.: intranasal; DMBA: 7,12-Dimethylbenz(a)anthracene; L-NAME: N-nitro-L-arginine-methylester; LPS: Lipopolysaccharide; LDL: low-density lipoprotein; STZ: Streptozotocin; CPQ: combination of curcumin with piperine and quercetin; HFD: high-fat diet; GSH: glutathione; SOD: superoxide dismutase; TC: total cholesterol; CR: caloric restriction; KC/GRO: Keratinocyte chemoattractant / growth-regulated oncogene chemokines; TG: triglyceride; OBX: olfactory bulbectomy; BaP: benzo(a)pyrene; LPO: lipid peroxides; TBARS: Thiobarbituric acid reactive substances ; GPx: glutathione peroxidase;; ROS: reactive oxygen species; HDL: high-density lipoprotein; CAT: catalase; GR: glutathione reductase; F/G: feed/gain ratio; DAO: diamine oxidase activity; mRNA: messenger RNA; QA: Quinolinic acid; IL: interleukin; TNF- α: tumor necrosis factor-alpha; DOPAC: 3, 4-dihydroxyphenylacetic acid; HVA: homovanillic acid; GABA: gama amino butric acid; 6-OHDA: 6-hydroxy dopamine; ApoAI: apolipoprotein AI; LCAT: lecithin cholesterol acyltransferase; CYP7A1: cholesterol 7α-hydroxylase; PCC: protein carbonyl content; LDLR: low-density lipoprotein receptor; CORT: corticosterone; CUS: chronic unpredictable stress; 8-oxo-dG: 8-oxo-2 -deoxyguanosine; GST: glutathione-S-transferase; MNPCEs: micronucleated polychromatic erythrocytes; EROD: ethoxyresorufin o-deethylase; PRO: pentoxyresorufin o-dependentylase; BaPDE-DNA adducts: benzo(a)pyrene-diol epoxide DNA adducts; QR: Quinone reductase;

Table 2. Summary of the clinical trial studies

Author/ Year/ Country	Sample size (Male/female)	Participants	Age Range (Years) ± mean	Intervention	Control	Duration	Findings
Non-alcoholic fatty liver disease							
Panahi, 2019, Iran (Panahi et al., 2019)	70(39/31)	Patients with NAFLD	47.7 ±2.35	5 mg/day piperine - 500 mg/day curcuminoids	Placebo	12 weeks	• Significant reduction in levels of albumin and NAFLD severity in intervention group vs placebo • BIL, TG, HDL-c, ferritin, LDL, FPG, HbA1c, BUN, Cr, TSH, WBC, RBC, Plt, ALT, AST, ALP, Hb, HCT, ESR, Fe, and TIBC did not change between groups
Mirhafez, 2019, Iran (Mirhafez et al., 2019)	47(29/18)	patients with NFLD	41.10 ±3.42	5 mg/day piperine - 500 mg/day curcuminoids	Placebo	8 weeks	• No significant changes in PAB values between groups.
Saberi-Karimian, 2020, Iran (Saberi-	55	Patients with NAFLD	18-70	5 mg/day piperine - 500 mg/day curcuminoids	Placebo	8 weeks	• Decrease in body weight and NAFLD severity according to the ultrasonography results in intervention group vs. placebo • Improvement in MCP-1 TNF-α, EGF levels in intervention group vs. placebo

Karimian et al., 2020)							
Mirhafez, 2021, Iran (Mirhafez et al., 2021)	79	Patients with NAFLD	18-65	5 mg/day piperine - 500 mg/day curcuminoids	Placebo	8 weeks	• Significant reduction in levels of ALP and NAFLD severity in intervention group vs placebo
				Type 2 diabetes mellitus			
Panahi, 2018, Iran (Panahi, Khalili, Sahebi, Namazi, Reiner, et al., 2017)	100(51/49)	Patients with T2DM	42±7.5	5 mg/day piperine - 500 mg/day curcuminoids	Placebo	12 Weeks	• Glucose, ALT, AST, HbA1c, C-peptide reduced in the intervention group vs. control • Weight and BMI significantly reduced with intervention • No changes in the factors below: insulin, hs-CRP, Cr, HOMA-IR, HOMA-β and HIS
Panahi, 2017, Iran (Panahi, Khalili, Sahebi, Namazi,	100(51/49)	Patients with T2DM	42±7.5	10 mg/day piperine + 1000 mg/day curcuminoids	Placebo	8 Weeks	• Serum SOD & TAC activities increased in intervention group, while MDA decreased vs. placebo group

Atkin, et al., 2017)							
Panahi, 2017, Iran (Panahi, Khalili, Sahebi, Namazi, Karimian, et al., 2017)	100	patients with T2DM		10 mg/day piperine + 1000 mg/day curcuminoids	Placebo	12 weeks	• Leptin, TNF-α and leptin: adiponectin ratio significantly decreased while adiponectin significantly increased in intervention group vs. placebo
Panahi, 2017, Iran (Panahi et al., 2018)	100(51/49)	patients with T2DM	42±7.5	10 mg/day piperine + 1000 mg/day curcuminoids	Placebo	12 weeks	• Serum levels of non-HDL, TC and Lp(a) significantly decreased and HDL increased in intervention group vs. placebo • TG and LDL-c did not change in the intervention group vs. control
Neta, 2021, Brazil (Neta et al., 2021)	71	patients with T2DM	-	5 mg/day piperine - 500 mg/day curcuminoids	placebo	120 days	• Significant reduction in glycaemia, HbA1c, HOMA index and TG level in intervention group vs. placebo
Metabolic syndrome							

Panahi, 2014, Iran (Panahi et al., 2014)	100(50/50)	patients with metabolic syndrome	44.13±9.17	1000 mg/day curcuminoids + 10 mg/day of Bioperine (extract of Piper sp. containing at least 95% piperine)	Placebo	8 weeks	• Significant reduction in TG, non-HDL-c, LDL-c, TC, and Lp(a) • Significant increase in HDL in the intervention group
Panahi, 2015, Iran (Yunes Panahi et al., 2015)	100(50/50)	patients with metabolic syndrome	44.13±9.17	10 mg/day piperine + 1000 mg/day curcuminoid	Placebo	8 weeks	• Increase in SOD activities and decrease in MDA & CRP levels vs. placebo.
Panahi, 2016, Iran (Yunes Panahi, Mahboobeh Sadat Hosseini, Nahid Khalili, Effat Naimi, Sara Saffar	100(50/50)	patients with metabolic syndrome	44.13±9.17	500 mg curcuminoids + 5 mg piperine twice a day	Placebo capsules contained the same amount of lactose + 5 mg piperine	8 weeks	• Serum adiponectin increased in the intervention group vs. placebo • Serum leptin concentrations, serum leptin:adiponectin ratio significantly decreased in intervention group vs. placebo

Soflaei, et al., 2016)							
Panahi, 2016, Iran (Yunes Panahi, Mahboobeh Sadat Hosseini, Nahid Khalili, Effat Naimi, Luis E Simental-Mendía, et al., 2016)	100(50/50)	patients with metabolic syndrome	44.13±9.17	500 mg curcuminoids + 5 mg piperine twice a day	Placebo capsules contained the same amount of lactose + 5 mg piperine	8 weeks	• Significant decrease in MCP-1, TGF-β, IL-6, TNF-α in the curcumin vs. placebo
				Obesity			
Mohajer, 2014, Iran (Mohajer et al., 2014)	30	obese subjects	39 ± 9.0	500 mg curcuminoids + 5 mg piperine twice a day	Placebo capsules contained only 5 mg piperine	4 weeks	• Significant increase was observed in serum Zn/Cu ratio and a reduction in Cu/ Zn ratio in the intervention group vs. placebo • No significant alteration was observed in serum concentrations of Zn, Cu and SOD activities.

Moohebati, 2014, Iran (Moohebati et al., 2014)	21(12/9)	obese dyslipidemic subjects	38.39± 11.35	5 mg/day piperine + 1000 mg/day curcuminoids	Placebo (5 mg piperine)	4 weeks	• No changes in LDL levels with curcuminoid supplementation
				Traumatic brain injury			
Shadnoush, 2020, Iran (Shadnoush et al., 2020)	62 (49/13)	critically ill patients with TBI	43.08 ± 15.63	5 mg/day piperine + 500 mg/day curcuminoids via enteral nutrition	Placebo via enteral nutrition	7 days	• Reduction in leptin levels in curcuminoids versus placebo group.
Zahedi, 2021, Iran (Zahedi et al., 2021)	62 (49/13)	critically ill patients with TBI	43.1 ± 15.6	5 mg/day piperine + 500 mg/day curcuminoids via enteral nutrition	Placebo (lactose) via enteral nutrition	7 days	• Significant reduction in CRP, MCP-1, TNF-α, IL-6 following curcuminoids consumption in comparison with placebo. • NUTRIC and APACHEII score significantly improved following curcuminoids consumption
				COVID-19 and other respiratory diseases			
Pawar, 2021, India (Pawar et al., 2021)	140(99/41)	patients with COVID-19	18-85	525mg curcumin with 2.5mg piperine in tablet twice a day	a dose of probiotics twice a day	14 days	• Ability to maintain oxygen saturation above 94% on room air, less deterioration, early symptomatic recovery and better clinical outcomes compared to control group.

							• Reduce the hospitalization duration in patients with moderate/severe symptoms, fewer mortality in the curcumin/piperine group
Askari, 2022, Iran (Askari et al., 2022)	46 (27/ 19)	outpatients with COVID-19	18-65	2 capsules each contained 500 mg curcumin + 5 mg piperine	2 placebo capsule; each contained 505 mg maltodextrin	14 days	• Significant improvement of weakness compared to placebo group • No significant changes in biochemical and clinical indices with curcumin-piperine
Panahi, 2016, Iran (Panahi, Ghanei, Hajhashemi, & Sahebkar, 2016)	78(78/0)	Chronic Pulmonary Complications Due to Sulfur Mustard exposure	52.47±8.05	1500 mg/day curcuminoids + 15 mg/day piperine	Placebo	4 weeks	• Significant increase in GSH and decrease in MDA • Significant improvement of CAT and SGRQ scores compared to placebo group
				Other diseases			
Mahato, 2019, India (Mahato et al., 2019)	40 (35/5)	Patients with OSMF	34.75± 11.53	A tablet comprised curcumin (500 mg), piperine (5 mg) and lycopene	-	12 weeks	• Significant improvement for post treatment reduction in VAS score for burning sensation and increase in MO, MF and TP. • Increase in the epithelial thickness decrease in collagen deposition.

				(25 mg) twice a day			
Kaur, 2017, India (S. Kaur et al., 2017)	60	Patients with moderate gingivitis	27.81± 7.56	SRP along with 300 mg curcumin, 5 mg piperine and 10 mg lycopene twice a day	SRP alone	3 weeks	• Both treatment groups displayed reduction in clinical parameters such as PI, GI and PPD but intervention group indicated greater reduction vs. control group.
Panahi, 2015, Iran (Panahi, Badeli, Karami, & Sahebkar, 2015)	111 (51/60)	patients with MDD	40.55± 9.78	standard antidepressive therapy + + 10 mg/day piperine + 1000 mg/day curcuminoids	standard antidepressive therapy alone	6 weeks	Intervention group had: • Significant reduction in total HADS score and subscales of anxiety & depression • Significant reduction in BDI-II total score and scores of somatic and cognitive subscales
Hatab, 2019, Egypt (Hatab et al., 2019)	20(16/4)	Patients with HCC	58.95±5.47	40 mg piperine 4 g curcumin and 500 mg taurine/ day	-	3 successive treatment cycles (each was a 30-day) with 24 months follow-up	• IL-10 and miR-21 levels were reduced

Delecroix, 2017, Australia (Delecroix et al., 2017)	16 (16/0)	Exercise Induced Muscle Damage	20.7 ± 1.4	20mg of piperine + 2g of curcumin three times a day	placebo	two phases of 4 days (starting 48 h preexercise and continuing until 48 h post-exercise)	• Curcumin & piperine supplementation before & after exercise shows an effect on the recovery of muscle function 24h & 48h after exercise
Volak, 2013, USA (Volak et al., 2013)	30	gut microbiota profiles of healthy human	19-58	turmeric tablets (1000 mg Curcuma longa + 1.25 mg black pepper (BioPerine)) or curcumin tablets (1000 mg of curcumin (Curcumin C3 Complex) + 1.25 mg BioPerine) 3 tablets twice a day	placebo	8 weeks	• Reduction in bacterial species by 15% in placebo group vs. 7% increase in turmeric-treated subjects. Participants using curcumin showed an average increase of 69% in species. • Multiple species belonging to a genus indicated concordant changes observed in treatment groups and not with placebo.

Khonche, 2016, Iran (Khonche et al., 2016)	60 (26/34)	patients with peptic ulcer	35.06+ 9.04	H. pylori eradication triple standard treatment along with 500 mg curcuminoids + 5 mg piperine	H. pylori eradication triple standard treatment along with placebo capsules contained microcrystalline cellulose +5 mg piperine	4 weeks	• Adjunctive therapy with curcumin significantly improved dyspepsia symptoms (HKDI score). • The participant numbers whose dyspepsia was improved with treatment was higher in the curcumin group in comparison to placebo • Equal rate of H. pylori eradication

hs-CRP: high-sensitivity C-reactive protein; IL: Interleukin; HbA1c: hemoglobin A1C; BMI: Body mass index; BUN: blood urea nitrogen; RBC: red blood cell; MDA: malondialdehyde; CAT: catalase; ALT: alanine aminotransferase; BIL: bilirubin; AST: aspartate aminotransferase; ALP: alkaline phosphatase; Cr: creatinine; ESR: erythrocyte sedimentation rate; HSI: hepatic steatotic index; FPG: fasting plasma glucose; Fe: iron; GSH: glutathione; Hb: hemoglobin; HCT: hematocrit; HDL-c: high density lipoprotein cholesterol; HOMA-IR: the homeostasis model assessment estimated insulin resistance; HOMA-β: the homeostasis model assessment-β cell function; LDL-c: low density lipoprotein cholesterol; Lp (a): lipoprotein (a); Plt: platelet; sdLDL-c: small dense low density lipoprotein cholesterol; SOD: superoxide dismutase; TAC: total antioxidant capacity; TG: triglycerides; TGF-b: transforming growth factor beta; TIBC: total iron-binding capacity; TSH: thyroid-stimulating hormone; WBC: white blood cell; TNF-α: tumour necrosis factor-α; VAS: visual Analog Scale; MO: mouth opening; MF: mucosal flexibility; TP: and tongue protrusion; OS: overall survival; miRNAs: MicroRNAs; PAB: pro-oxidant and antioxidant balance; SGRQ: St. George respiratory Questionnaire; HRQoL: health-related quality of life; NFLD: Non-alcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; OSMF: Oral submucous fibrosis; HCC: hepatocellular carcinoma; MDD: major depressive disorder; ICU: Intensive Care Unit; MCP-1: monocyte chemo attractant protein-1; non-HDL-c: non-high density lipoprotein cholesterol; EGF: epidermal growth factor; HADS: Hospital Anxiety and Depression Scale; BDI-II: Beck Depression Inventory II; PPD: Probing pocket depth; PI: Plaque index; SRP: scaling and root planning; GI: Gingival index; SOD: superoxide dismutase; Cu: copper; Zn: zinc; TBI: traumatic brain injury; HKDI: Hong Kong dyspepsia index;

MCP-1: monocyte chemoattractant protein-1; APACHEII: Acute Physiology and Chronic Health Evaluation II; NUTRIC: Nutrition Risk in Critically ill; GPx: glutathione peroxidase

Table 3. List of clinical trials using curcumin piperine (www.irct.ir and www.clinicaltrials.gov).

IRCT Number/ NCT identified	Title	Disease	Study design	Number of Participants	Agent	Dose	Duration	Main Outcomes	Location	Phase
IRCT 2012121601 1763N42	Curcumin-Piperine on cardiometabolic factors, hepatic steatosis and fibrosis of fibroscan - NAFLD	NAFLD	RCT	60	Curcumin piperine	500 mg curcumin + 5 mg piperine	12 weeks	TG; TC; HDL; LDL; Weight; BMI; Waist circumference; FBS; ALT; AST; Hepatic steatosis and fibrosis	Iran	N/A
IRCT 2015052322 381N1	Curcumin in patients with NAFLD	NAFLD	Double blind placebo controlled RCT	40	Curcumin piperine	Curcumin C3 complexTM (500 mg) plus BioperineTM (5 mg, patented extract obtained from black pepper fruits (Piper nigrum) standardized minimum to 95% Piperine.	2 months	NAFLD grade, liver function tests	Iran	3

IRCT 20121 21601 1763 N47	Curcumin plus piperine - cardiometabolic risk and fibroscan - non-alcoholic steatohepatitis (NASH)	NASH	RCT	60	Curcu min piperi ne	5 mg piperine + 500 mg curcumin	12 weeks	TG; TC; HDL; LDL; Weight; BMI; Waist circumference; FBS; ALT; AST; Hepatic steatosis and fibrosis, Hs-CRP, BP	Iran	N / A
IRCT 20121 21601 1763 N50	Curcumin + piperine in diabetic people and hypertriglyceridemia	Patients with T2DM and hypertriglyce ridemia	RCT	80	Curcu min piperi ne	500 mg curcumin + 5 mg piperine	12 weeks	Lipid profile (HDL, LDL, TG, TC); fasting blood sugar (FBS); weight, height, waist circumference, BMI; blood pressure; insulin level; CRP	Iran	3
IRCT 20170 12332 132N 1	Curcumin + piperine and gingerol on sudden sensorineural hearing loss in diabetic patients	Diabetes	Randomized triple blind placebo-controlled trial	51	Curcu min-piperi n and ginger ol	Two capsules, each contained: 300 mg of curcumin , 3.25 mg Piperine and 7.5 mg of gingerol	2 months	Changes in hearing threshold	Iran	N / A
IRCT 20120 70101 0149 N3	Curcumin + piperine in rheumatoid arthritis	RA	RCT	60	Curcu min piperi ne	500 mg curcumin + 5 mg piperine	12 weeks	Anthropometry and clinical signs in patients with rheumatoid arthritis	Iran	3

IRCT 20121 21601 1763 N53	Curcumin + piperine in rheumatoid arthritis	RA	RCT	60	Curcumin piperine	500 mg curcumin + 5 mg piperine	12 weeks	TC, TG, LDL, HDL (FBS) clinical signs, body inflammation index (hs-CRP) and ESR)) and mean DASS score	Iran	3
IRCT 20200 51404 7445 N1	Curcumin + piperine supplementation in covid-19	COVID-19	RCT	60	Curcumin piperine	3 curcumin capsules (500mg)	2 weeks	CT-scan findings; Hospitalization duration; CBC; LDH; PT; PTT; D-DIMER; BUN / CR.	Iran	3
IRCT 20121 21601 1763 N52	Curcumin + piperine in coronavirus patients admitted to ICU	COVID-19	RCT	50	Curcumin piperine	3 capsules; each contained 500 mg curcumin + 5 mg piperine	7 days	Body temperature, ESR and CRP, length of hospital stay, extent and severity of patients' cough, (ALT, AST, LDH), (BUN, Creatinine), (CBC), NUTRIC score, APACHE II and SOFA score, mean blood sugar, albumin	Iran	3
IRCT 20130 91114 521N 2	Curcumin in patients with sulfur mustard exposure	Chronic respiratory complications due to sulfur mustard exposure	RCT	80	Curcumin piperine	Curcumin (150 mg/day) and piperine (15 mg/day)	4 weeks	Spirometric parameters and quality of life	Iran	2-3

IRCT20080901001165N43	The curcumin's effect in patients with colorectal cancer under chemotrapy in comparison with placebo group	Colorectal cancer	RCT	36	Curcumin piperine	500 mg curcumin + 5 mg piperine	8 weeks	TNF-alpha; IL-6; Quality of life score	Iran	2
NCT04731844	Curcumin + piperine in Patients on Active Surveillance for either MGUS, low-risk SMM or early stage prostate cancer	Prostate Cancer, Multiple Myeloma, SMM MGUS	Non-Randomized-open labeled clinical trial	40	Curcumin + Piperine (Curcumin C3 Complex®)	4 gram/5mg orally BID	12 months	1) Response rate 2) Measure of time from study enrollment until response	United States, New York	2
NCT02598726	Curcumin + piperine in ureteral stent-induced symptoms in cancer patients	Bladder Spasm, Malignant, Neoplasm, Pain, Urinary Urgency	Clinical Trial	9	Curcumin piperine	-	7 days	Incidence of adverse events MTD of curcumin + piperine Optimal biologically active dose for Curcumin + piperine (standardized)	United States	1
IRCT20180619040151N1	Curcumin in patients with TBI receiving Enteral Nutrition at Intensive Care Unit	TBI	RCT	52	Curcuminoids + piperine	Curcuminoids in combination with 5 mg piperine	7 days	Inflammatory markers; oxidative stress markers; adipokines; NUTRIC score; SOFA score	Iran	3

IRCT 20201 12904 9534 N4	Effectiveness of curcumin-piperine on inflammatory factors, cardiac biomarkers, atrial fibrillation and clinical outcomes after coronary artery bypass graft surgery (CABG)	CABG	RCT	60	Curcu min piperi ne	a) 500 mg curcumin + 5 mg piperine b) 10 mg piperine + 1000 mg curcumin c) 1500 mg curcumin + 15 mg piperine	5 days	Inflammatory factors, cardiac biomarkers, and atrial fibrillation.	Iran	3
IRCT 20121 21601 1763 N48	Curcumin + piperine in ischemic stroke in the rehabilitation phase	Ischemic stroke	RCT	80	Curcu min piperi ne	500 mg curcumin + 5 mg piperine	12 weeks	TG; TC; HDL; LDL; Weight; BMI; Waist circumference; Total antioxidant capacity; Fibrinogen; Hs-CRP; BP	Iran	3
IRCT 20150 61302 2681 N4	Curcumin + piperine in sepsis patients admitted to ICU	Sepsis	RCT	50	Curcu min piperi ne	2 capsules; each contained 500 mg curcumin + 5 mg piperine	14 days	Inflammation and infection in patients with sepsis in the ICU	Iran	2-3
NCT0 34750 17	Effects of Curcumin in CKD	CKD	Randomized crossover controlled clinical study	30	3 curcu min piperi ne	Each capsule: 500mg of curcumin	4 weeks	1. Antioxidants and anti-inflammatory biomarkers		

					capsules	and 5mg of piperine		2. Inflammatory biomarkers		
NCT04048031	Nutraceutical Supplement With Standardized Botanicals on hair thinning	Peri-menopausal and Menopausal Women	Randomized parallel	70	BCM-95 BioCurcumin, Saw Palmetto, EVNolMax 20% Tocotrienol/ Tocopherol complex, gelatinized Maca, Astaxanthin, Bioperine (piperine)	-	6 months	Number of terminal vellus and total hairs in the Target Area	United States	N/A

NCT001816 62	Evaluation of Naturally Occurring Inhibitors of UDP-glucuronyltransferase on the oral bioavailability of curcumin	Healthy volunteers	Crossover Assignment	6	Curcumin, piperine, silybin	4 gm of single oral dose curcumin as either alone or with piperine or with silybin	Single oral dose	Curcumin pharmacology	United states	N/A
NCT036218 65	Pharmacokinetic Study to Evaluate a New Formulation to Enhance Curcuminoids Bioavailability (TURBIO)	Healthy volunteers	Randomized cross-over clinical trial	30	Turmeric extract C3 complex® 95% curcuminoids + BioPerine® 95% piperine	1500 mg curcumin + 15 mg piperine	24 hours	Primary endpoint - dose-normalized AUC of total curcuminoids Primary comparison is Turmipure Gold 300 mg versus Standard turmeric 1500 mg powder extract.	France	N/A

TG: triglyceride; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; TC: total cholesterol;; TBARS: Thiobarbituric acid reactive substances; GPx: glutathione peroxidase; ALP: alkaline phosphatase; IL: interleukin; TNF- α: tumor necrosis factor-alpha: AST: aspartate aminotransferase; BMI: Body mass index; BUN: blood urea nitrogen; MDA: malondialdehyde; NUTRIC: Nutrition Risk in Critically ill; ALT: alanine aminotransferase; ESR: erythrocyte sedimentation rate; TAC: total antioxidant capacity; APACHEII: Acute Physiology and Chronic Health Evaluation II; MCP-1: monocyte chemo attractant protein; BP: blood pressure; CBC: cell blood count; DASS: Depression Anxiety Stress Scales; SOFA: Sequential Organ Failure Assessment; Nrf2: nuclear receptor factor 2; HO-1: heme oxygenase-1; NFkB: factor nuclear kappa B. RCT (randomized double blind placebo-controlled trial); non-alcoholic fatty liver disease (NAFLD); Intensive care unit (ICU);

Traumatic Brain Injury (TBI); Smoldering Multiple Myeloma (SMM); Monoclonal Gammopathy of Unknown Significance (MGUS); Maximum tolerated dose (MTD); Chronic Kidney Disease (CKD)