REVIEW ARTICLE

Safety and Efficacy of Turmeric (*Curcuma longa*) Extract and Curcumin Supplements in Musculoskeletal Health: A Systematic Review and Meta-Analysis

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ABSTRACT

Context • Turmeric is a well-known herb that has been used in many traditional medicinal systems since ancient times. Turmeric roots contain hydrophobic polyphenols called curcuminoids, which have proven anti-inflammatory and antioxidant effects and are shown to be beneficial for the management of musculoskeletal health. Various products containing curcumin or turmeric extract are commercially available.

Objective • This systematic review and meta-analysis of randomized clinical trials (RCTs) is intended to evaluate the effective dose, safety, and efficacy of commercial turmeric extract and curcumin supplements in musculoskeletal health.

Design • The research team performed a systematic literature search of PubMed, Google Scholar, and Cochrane Library databases and conducted a meta-analysis according to PRISMA guidelines.

Setting • Authors from India and USA contributed to this systematic review and meta-analysis.

Results • The research team analyzed 20 prospective, randomized clinical studies, of which seven studies were focused on skeletal muscle health and thirteen on joint health. Statistical heterogeneity was established based on the results of heterogeneity analysis of a Chi-square (χ^2) value for Cochran's Q statistic of 29.3765 for musculoskeletal and 3666.80 for joint health studies ($P < .0001$ for both analyses). Therefore, the random effects model was used. The χ^2 value of the random effects model was 216.5545 for skeletal muscle health studies and 1400.65 for joint health studies, which was statistically significant with $P < .0001$ for both analyses.

Conclusions • Turmeric extract and curcumin supplements can be effective adjuvants for the management of musculoskeletal health, with a low incidence of AEs. The water-dispersible turmeric extract, WDTE60N, at a dose of 250 mg per day, was found to be more effective than other curcumin products. However, the studies included in the analysis were conducted using diverse doses and treatment durations. Further evaluation using comparisons in future clinical trials can establish the appropriate effective dose of curcumin supplements for the overall maintenance of musculoskeletal health. (*Altern Ther Health Med.* 2023;29(6):12-24).

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Botanicals and herbs have been used throughout human history for consumption as delicacies, and more important, for their health benefits, owing to their biological or pharmacological applications.[1] Many of these herbs and botanicals have been extensively studied, with increasing evidence of their therapeutic applications and health benefits, and they are considered valuable ingredients in the nutraceutical sector.

The term nutraceuticals refers to specialized foods or food-derived products that provide health and medical benefits, including the prevention and treatment of diseases,

without major adverse effects (AEs).[2,3] Turmeric or Curcuma longa is a nutraceutical, a natural herbal ingredient with medicinal properties1 that provides multiple health benefits.

Curcuma longa is a rhizomatous, herbaceous, perennial herb belonging to the ginger family and has a broad variety of biological properties, such as antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties.[4,5] These properties belong to the bioactive principles in the rhizomes, the hydrophobic polyphenols called curcuminoids, which comprise curcumin, demethoxycurcumin, and bisdemethoxycurcumin,[6] of which curcumin—1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione—is the major natural polyphenol.

Curcuminoids, commonly called curcumin, have been shown to exhibit a broad spectrum of pharmacological actions proven in several in-vitro and in-vivo studies as well as in clinical trials.[6] Curcumin has also been recognized as safe by the US Food and Drug Administration (FDA).[7]

The musculoskeletal system relates to an individual's mobility and dexterity. It comprises muscles, bones, joints, and adjacent connective tissue. It plays a major role in mobility and is important in maintaining an active, productive, and prolonged working life.[8] Common musculoskeletal conditions that often hamper the body's mobility include osteoarthritis (OA), rheumatoid arthritis (RA), lower back pain (LBP), and osteoporosis (OP)[9,10] as well as acute conditions, such as delayed onset muscle soreness (DOMS).

DOMS is a constellation of muscular pain and stiffness that occurs in healthy individuals several hours after undergoing unaccustomed exercise. It is caused by eccentric muscle activity associated with inflammatory responses and the production of reactive oxygen species (ROS) that cause inflammation and oxidative stress.[9-11]

Musculoskeletal disorders cause the highest global burden on individuals, health, and social-care systems. According to the Global Burden of Disease (GBD) Study, as of 2019, 1.71 billion cases of musculoskeletal disorders have been reported globally.[12] Lower back pain was the most prevalent (36.8%), followed by other musculoskeletal disorders (21.5%), OA (19.3%), neck pain (18.4%), gout (2.6%), and RA (1.3%).[11]

According to the World Health Organization (WHO) statement in July 2022, musculoskeletal conditions, along with increasing the risk in non-communicable diseases, are also the highest contributor to the global need for rehabilitation, which accounts for approximately two-thirds of all adults in need of rehabilitation. Individuals with musculoskeletal conditions are also at a higher risk of developing mental health issues.[12]

According to a systematic analysis of the Global Burden of Disease Study, as of 2015, musculoskeletal disorders were a leading cause of disability worldwide and a long-term burden from the sequelae of fractures and dislocations.[13] Considering these data, effective management of musculoskeletal diseases is important.[14]

The first-line management of musculoskeletal health conditions includes analgesics, such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs). However, these drugs have low and transient analgesic effects, and several studies have observed AEs, especially in senior patients with pre-existing comorbidities. In particular, the safety of NSAIDs remains a concern when selecting a dose regimen for patients.[11]

The long-term use of NSAIDs can cause gastrointestinal disorders, such as dyspepsia, ulcers, bleeding, and perforation as well as cardiovascular, and kidney problems.[14] These factors contribute to the increased need for alternative options for managing musculoskeletal conditions, such as dietary supplements and natural products.[4]

Curcumin is one such option that has shown the potential for improving musculoskeletal health due to its anti-inflammatory action, as observed in many in-vitro and in-vivo studies as well as in clinical trials. Curcumin has demonstrated efficacy in reducing the impact of DOMS, as suggested by its effects on pain intensity and muscle injury,[13] and its anti-arthritic effects, include inhibition of joint inflammation and periarticular joint destruction.[1]

Mechanism of Action

Curcumin is a pleiotropic molecule that has multiple mechanisms of action. It inhibits mRNA expression of inflammatory mediators, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and matrix metalloproteinases (MMPs), which play an important role in musculoskeletal disorders through various pathways.[5]

Curcumin alters enzyme activities, growth factor receptors, co-factors, and other molecules,[15] including protecting IL-1β-induced apoptotic chondrocytes, decreasing the early degenerative changes of articular cartilage, and inhibiting cytoplasmic phospholipase A2 (cPLA2), cyclooxygenase 2 (COX-2), and 5-lipoxygenase (5-LOX) pathways.[16]

Curcumin helps reduce muscle pain and muscle damage, as evidenced by the reduction in lactate dehydrogenase (LDH) levels and ensures faster muscle recovery. It exerts an anti-inflammatory effect by modulating pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-8, and exerts an antioxidant effect.[17]

Current Review and Meta-analysis

This systematic review and meta-analysis of randomized clinical trials (RCTs) is intended to evaluate the effective dose, safety, and efficacy of commercial turmeric extract and curcumin supplements in musculoskeletal health.

METHODS

Procedures

The data for this meta-analysis were reviewed and analyzed by the authors from India and the USA.

Search strategy and selection criteria. The research team performed the systematic review by searching PubMed,

Google Scholar, and Cochrane Library databases and conducted a meta-analysis according to PRISMA guidelines.[18]

The review and meta-analysis included studies if they: (1) were prospective RCTs; (2) evaluated the safety, efficacy, and effective dose of curcumin for musculoskeletal health; and (3) recruited participants older than 18 years of age who were either healthy or had reported musculoskeletal disorders.

The review and meta-analysis excluded studies if they used no musculoskeletal health indications, or if they used a study design other than RCT.

As search terms, the electronic searches used medical subject headings (MeSH) terms and the corresponding keywords. The search terms used were (MeSH "Curcuma," "Curcumin" and keywords "curcuma," "turmeric," "turmeric extract," "curcumin," "curcuminoid"), and (MeSH "Arthritis," "Osteoarthritis," "knee osteoarthritis," "rheumatoid arthritis" and the keywords were "arthritis," "osteoarthritis," "musculoskeletal disorders," "DOMS," "muscle soreness").

Additionally, the research team manually checked the bibliographies of the identified articles, including relevant systematic reviews and meta-analyses, to identify additional eligible studies.

Search

The research team identified 1540 records through Google Scholar, followed by 370 from PubMed and 73 from Cochrane database. Forty-two records were included after removing duplicates, of which 22 were excluded because they didn't meet the required criteria. Ultimately, 20 prospective RCTs were included in this systematic review and meta-analysis (Figure 1).

Of those 20 prospective RCTs that evaluated the efficacy and safety of curcumin, seven studies were related to skeletal muscle health and 13 studies were related to joint conditions.

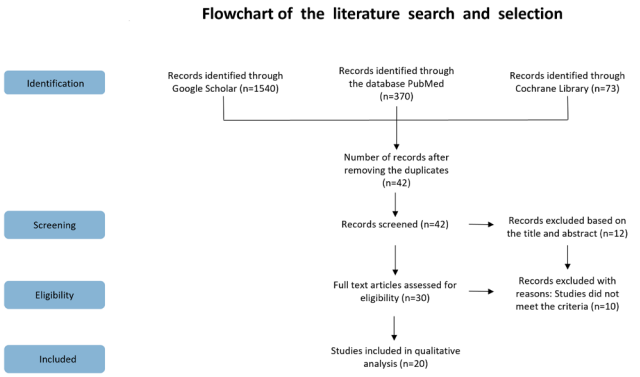
Muscle Health: Systematic Review

Table 1 shows the characteristics of the included studies.

Mallard et al.[19] These researchers conducted a randomized, double-blind, placebo-controlled study over three days to assess the effects of a commercial, cold-water-dispersible curcumin, HydroCurc, on exercise recovery when consumed as a drink by recreationally trained, healthy males. The study included 28 healthy males with strength-training experience. Participants received a single dose of 1000 mg of powder containing 500 mg of HydroCurc, which contains 427 mg of curcuminoids, or a matched placebo drink. The supplement was dispersed in 250 ml of water, pre-exercise and at 24 hours and 48 hours postexercise.

Pain was evaluated using a visual analog scale (VAS), as was thigh circumference (TC), lactates, creatine kinase (CK), LDH, high-sensitivity C-reactive protein (HS-CRP), myoglobin (Mb), IL-6, IL-10, and TNF-α levels. At 48-h and 72-h postexercise, higher muscle pain was reported in the placebo group than in the curcumin group, which suggests that the curcumin treatment might provide a quicker return to exercise training than the placebo, by reducing postexercise pain, modulating inflammatory pathways, and reducing lactate accumulation.

Figure 1. Flowchart of the literature search and selection



The IL-6 levels were significantly higher at one hour ($P < .05$), 24 h ($P < .01$), and 72 h ($P < .05$) postexercise in the curcumin group than in the placebo group. No significant differences were observed between the groups for CK, LDH, Mb, HS-CRP, or TNF-α levels at any time point.

Thanawala et al.[20] These researchers conducted a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of a commercial supplement, a Natural, Water-Dispersible Turmeric Extract (WDTE60N) TurmXTRA 60N, on DOMS in comparison with a placebo for 30 recreationally active, healthy participants. Participants were randomly assigned to receive a 250-mg capsule, containing 150 mg of curcuminoids or a placebo, once daily for 33 days, with a pre-exercise period of 29 days and a postexercise period of 4 days.

Pain intensity was assessed using a VAS scale and measured before and immediately after exercise and at 12, 24, 48, 72, and 96 h after eccentric exercise. Participants' well-being was assessed using the adapted version of the Hooper and MacKinnon questionnaire at the same time points.21 The muscle-damage markers serum CK and serum LDH were measured at baseline and at 24, 48, 72, and 96 h after eccentric exercise.

The turmeric extract group reported significantly less pain after eccentric exercise compared to the placebo group, based on the VAS score at the 12-hour time point. For all of the adapted Hooper and MacKinnon questionnaire's subdomains—fatigue, mood, general muscle soreness, sleep quality, and stress, the turmeric extract group demonstrated significantly greater improvement postexercise including overall well-being, compared to the placebo group.

A decrease in serum CK levels and significantly lower serum LDH levels were also observed in the turmeric extract group compared to the placebo group. The study showed that an intake of a water dispersible turmeric extract before and after eccentric exercise could significantly reduce subjective perceptions of pain and muscle soreness as well as serum LDH activity, and the extract also significantly improved sleep quality and psychological well-being in recreationally active participants compared to placebo.

Jäger et al.[22] These researchers conducted a randomized, double-blind, placebo-controlled study to examine the effects

Table 1. Safety and Efficacy of Monotherapy With Turmeric Extracts and Curcumin Supplements in Exercise-related Skeletal-muscle Health. None of the studies reported an adverse event.

Study	Sample Size	Age, y	Treatment	Curcuminoids/ Curcumin Administered Daily	Indication	Duration	Scale	Mean ± SD	Efficacy
Mallard et al, 2020[19]	Intervention group (n=13) Placebo group (n =14)	18-35	Single daily dose of 1000 mg of powder containing 500 mg of cold-water dispersible curcumin in 250 ml of water	427 mg of curcuminoids	Muscle soreness and postexercise lactate accumulation	3 days	VAS	VAS scores not provided in the publication	• Curcumin supplementation significantly reduced DOMS pain at 48 and 72 h postexercise compared to the placebo group. • Curcumin helped in reducing postexercise pain, modulating inflammatory pathways, and reducing lactate accumulation in an exercising population.
Thanawala et al, 2022[20]	Intervention group (n=15) Placebo group (n =15)	18-35	250 mg of natural, water-dispersible turmeric extract in capsule, once daily	150 mg curcuminoids	DOMS	33 days	VAS (hrs) Intervention: 12, 24, 48, 72, 96, Placebo: 12, 24, 48, 72, 96	Intervention (hrs): 12 4.0 ± 0.7 24: 5.0 ± 0.8 48: 3.3 ± 0.7 72: 1.9 ± 0.7 96: 0.7 ± 0.5 Placebo (hrs): 12: 4.5 ± 0.6 24: 5.9 ± 0.5 48: 5.5 ± 0.6 72: 4.5 ± 0.6 96: 3.3 ± 0.5	• In intervention group, lower pain was evident within 12 hours of eccentric exercise, thus indicating faster recovery. • Significantly reduced muscle soreness postintervention
Jager et al, 2019[21]	Intervention LD group (n=20) Intervention HD group (n=22) Placebo group (n=21)	19-29	LD: 250 mg daily of curcumin, HD: 1000 mg daily of curcumin	LD: 50 mg of curcuminoids HD: 200 mg of curcuminoids	Muscle-damaging exercise	56 days	VAS	VAS scores not provided in the publication.	• In 50-mg curcuminoids group, observed decreases in peak extension torque values occurred at one and 24 h after muscle-damaging exercise. • In 200-mg curcuminoids group, attenuated reductions occurred in some but not all participants.
Tanabe et al, 2019[22]	Intervention PRE group (n=8) Test POST group (n= 8) Placebo group (n=8)	_	90 mg twice daily of surface-controlled water-dispersible curcumin, for 180 mg/ day	64.8 mg of curcuminoids.	Exercise-induced muscle soreness	4 days	VAS	VAS scores not provided in the publication.	• Muscle soreness was lower at 3 days after exercise. • Curcumin ingestion after exercise had a more beneficial effect in attenuating muscle soreness.
Amalraj et al, 2020[24]	Intervention group (n=15) Placebo group (n=15)	≥20	500 mg once daily of turmeric matrix formulated in a capsule	250 mg of curcuminoids	DOMS, induced by eccentric continuous exercise	4 days	VAS	Intervention Screening: 2.90 ± 0.39 Visit: 5: 1.17 ± 0.52 Placebo Screening: 2.70 ± 0.46 Visit 5: 2.37 ± 0.48	• After 4 days, the curcumin formulation improved recovery and reduction of DOMS, without any side effects.
Drobnic et al, 2014[10]	Intervention group (n=9) Placebo group (n=10)	_	1000 mg of curcumin-phosphatidylcholine complex twice daily, for 2000 mg/day	400 mg of curcumin	DOMS	4 days	Pain intensity point scale (0-4)	Intervention: 23.3 ± 7.9 (17.2; 29.4) Placebo: 30.6 ± 7.9 (24.9;36.2)	• After 4 days, curcumin was effective in preventing DOMS by reducing pain intensity and muscle injury.
Wang et al, 2019[26]	Intervention group (n=6) Placebo group (n=6)	21 (avg age)	1500 mg daily of NCE extract	230.9 mg of curcumin	Injury risk on drop jumps	28 days	No pain assessment endpoint	_	• After 28 days of supplementation, NCE was effective, providing a variety of benefits for athletes.

Abbreviations: DOMS, delayed-onset muscle soreness; HD, high dose; LD, low dose; NCE, Nanobubbles water curcumin extract; VAS, Visual analogue scale.

of a commercial curcumin supplement, CurcuWIN. The study examined the effects of a low dose of 250 mg test product, containing 50 mg curcuminoids, and of a high dose of 1000 mg test product, containing 200 mg of curcuminoids, on blood flow, exercise performance, and muscle damage in physically active individuals.

The 63 eligible participants, divided into 3 groups, were randomly assigned to ingest a low dose or a high dose of the supplement or a placebo daily for 8 weeks. Muscle function, as measured using isokinetic dynamometry, and perceived soreness were assessed at baseline and at one, 24, 48, and 72 hours after a downhill run.

Nonsignificant improvements in total soreness were observed in the 1000-mg group. When compared to the placebo group, that group showed attenuated reductions for some, but not all, outcome measures for performance and soreness after completion of a downhill running bout. Additionally, the 250-mg dose didn't offer any advantage over the changes observed in the placebo and 1000-mg groups.

Tanabe et al.[23] These researchers performed a randomized, single-blind, parallel study to determine the effects before and after exercise of a commercial, surface-controlled water-dispersible curcumin, Theracurmin, on the changes in muscle-damage markers after eccentric exercise.

The 24 participants were randomly assigned to one of three groups. The two intervention groups received 90 mg twice daily, or 180 mg/d, of the test product, containing 32.4 mg curcuminoids: (1) the PRE group, for 7 days before exercise, and (2) the POST group, for 4 days after exercise. The CON group received a placebo for 4 days after exercise.

The maximal voluntary contraction (MVC) torque of the elbow flexors, elbow joint range of motion (ROM), muscle soreness, and serum creatine kinase (CK) activity were measured at baseline, immediately after, and at 1, 2, 3, and 4 days after exercise. In the POST group, ROM was higher at 3-4 days and muscle soreness was lower at 3 days after exercise than in the CON group ($P < .05$). However, in the PRE group, no significant differences existed in ROM and muscle soreness compared to those in the CON group after exercise. Additionally, no significant differences existed between the groups in terms of changes in MVC torque or serum CK activity.

Amalraj et al.[24] These researchers conducted a randomized, placebo-controlled, double-blind clinical study to test the efficacy of a commercial, complete natural turmeric matrix formulation, Cureit, in decreasing damage from oxidative stress and inflammation related to severe muscle damage induced by eccentric continuous exercise. The 30 participants were randomly assigned to one of two treatment groups and took either a 500 mg capsule of the test product, containing 250 mg of curcuminoids, or a placebo for 4 days.

Pain reduction was assessed using a VAS. No significant reduction in the VAS scores for pain occurred between baseline and postintervention for the participants treated with curcumin, and no significant differences were observed in the placebo group. The oral consumption of curcumin significantly reduced DOMS and caused a nonsignificant reduction in CK concentrations and a slight increase in the VO2 max value as compared with the placebo.

Drobnic et al.[10] These researchers performed a randomized, placebo-controlled, single-blinded, pilot study to examine whether a commercial, curcumin-phosphatidylcholine complex, Meriva, could attenuate damage from oxidative stress and inflammation related to acute muscle injury induced by eccentric continuous exercise. The 20 male participants were randomly assigned to receive either 1000 mg of the test product, containing 200 mg of curcumin, or a matching placebo, both twice daily.

Supplementation was initiated at 48 h prior to the test and continued for 24 h after exercise. Muscle damage was quantified by magnetic resonance imaging (MRI), laboratory tests, and histological analyses of muscle samples obtained at 48 h after the exercise. Pain intensity was recorded using a pain-intensity scale (0-4). Participants in the curcumin group reported less pain in the lower limbs than those in the placebo group, and the results were significant only for the right and left anterior thighs out of the three compartments evaluated—anterior, posterior, and medial.

Significantly fewer participants in the curcumin group had MRI evidence of muscle injury in the posterior or medial compartments of either thigh. No significant differences existed in the levels of the muscle-damage markers CK, HS-CRP, and monocyte chemoattractant protein-1 (MCP-1) in either group postintervention, except IL-8, which was significantly lower in the curcumin group only at 2 h after exercise. No differences in oxidative stress markers or muscle histology were observed.

Wang et al.[25] These researchers conducted a study to evaluate the effects of nanobubbles water curcumin extract (NCE) on reducing the risk of musculoskeletal injury in 12 female participants. Participants were randomly assigned to receive either 1500 mg of NCE, containing 230.9 mg curcumin, or a placebo daily for 4 weeks. Postintervention, the muscle-strength indices, contact time, significantly increased for the 100% drop jumps.

The levels of the muscle-damage marker CK weren't significantly different between the placebo and NCE groups. Postintervention, the NCE supplementation had decreased the peak vertical ground reaction force (PVGRF) during drop jumps, which might help reduce the risk of injury for drop jumps.

Muscle Health: Meta-analysis

For participants aged 18-35 years, who were treated with monotherapy using turmeric extracts and curcumin supplements, pain intensity was assessed using a VAS or a pain intensity point scale. Curcumin was effective and well-tolerated in reducing pain intensity. The water dispersible turmeric extract demonstrated significant reductions in pain intensity within 12 h postexercise, compared to other turmeric extract and curcumin supplements. Thus, the water dispersible turmeric extract proved to be more effective and safer than other turmeric extracts and curcumin supplements for the management of exercise-related skeletal muscle health.

Statistical Analysis

The research team analyzed the data in the meta-analysis using NCSS 2021 statistical software (Utah, USA). The Odds Ratio (OR) or Mean Difference (MD) and the 95% Confidence Intervals (CIs) were used as the efficacy and safety statistics. The Chi-square (χ^2) test was used to evaluate the heterogeneity in the literature. If the studies weren't heterogeneous, they were analyzed using a fixed-effects model; if they were heterogeneous, a random-effects model was used.

Two RCTs that studied DOMS and that used supplements that were either a water dispersible turmeric extract or a turmeric matrix formulation, had used VAS to evaluate pain as an efficacy parameter and were included in the analysis.

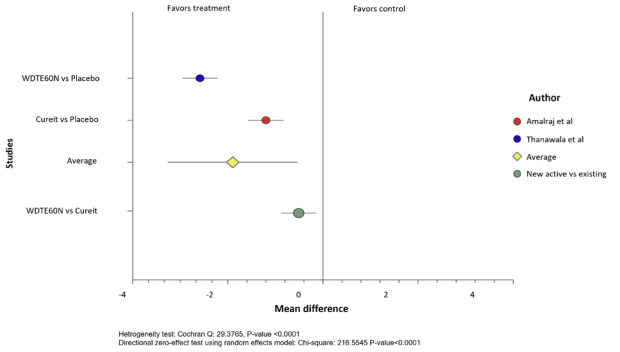
Results

The heterogeneity analysis found an χ^2 value for Cochran's Q statistic of 29.3765 and $P < .0001$, which showed that statistical heterogeneity existed between the two studies; therefore, the random effects model was used. The χ^2 value of the random effects model was 216.5545 with $P < .0001$, which was statistically significant. Table 2 shows that the difference between the intervention and control groups was significant [SMD -1.9 (-3.27; -0.53), $P < .00001$.

Table 2. Efficacy of Turmeric Extracts and Curcumin Supplements in Exercise-related Skeletal Muscles Health Using Random Effect Model

Product Comparison	Mean Difference	Standard Error	95% CI	Weightage %
Intervention vs Comparator				
Amalraj et al[24]: turmeric matrix formulation and placebo	-1.2	0.18	[-1.57, -0.83]	50.00
Thanawala et al[27]: water dispersible turmeric extract and placebo	-2.6	0.18	[-2.97, -2.23]	50.00
Combined				
Average	-1.9	0.7	[-3.27, -0.53]	
New vs existing treatment: water dispersible turmeric extract vs turmeric matrix formulation	-0.47	0.19	[-0.85, -0.09]	

Figure 2. Forest plot showing the Efficacy in Musculoskeletal Health



In addition, when comparing the efficacy between the water dispersible turmeric extract and the turmeric matrix formulation using VAS for pain as an efficacy parameter, the meta-analysis showed a statistically significant difference between the two groups [SMD -0.47 (-0.85; -0.09), $P = .0116$].

The differences between the water dispersible turmeric extract and the placebo and between the turmeric matrix formulation and the placebo were statistically significant, with [SMD -1.2 (-1.5743, -0.8252), $P < .00001$] and [SMD -2.6 (-2.974, -2.226), $P < .00001$], respectively.

The forest plot shows the results of each study in a single plot (Figure 2). The size of the plot symbols is proportional to the sample size of the study. The points on the plot are sorted by study and mean difference. The lines represent the confidence intervals for the mean differences. A narrow confidence interval indicates a greater degree of precision.

Joint Health: Systematic Review

The most common joint health disorders include chronic knee pain, knee OA, and RA. The effects of curcumin on joint health and these disorders have been evaluated in several clinical trials pertaining to its potent anti-inflammatory action. Tables 3 and 4 show the characteristics of the included studies.

Thanawala et al.[26] These researchers conducted a double-blind, randomized, placebo-controlled, parallel-group study of healthy participants with chronic knee pain

Table 3. Safety and Efficacy of Monotherapy With Turmeric Extracts and Curcumin Supplements for Joint Health, Using VAS Scale

Study	Sample Size	Age, y	Treatment	Curcuminoids / Curcumin Administered Daily	Indication	Duration	Scale	Mean ± SD	AE/ safety	Efficacy
Thanawala et al, 2021[27]	Intervention group (n=53) Placebo group (n=53)	18-60	250 mg once daily of water dispersible turmeric extract in capsule	150 mg of curcuminoids	Chronic knee pain	90 days	VAS Baseline to day 90	Intervention Baseline: 5.4 ± 0.9 Day 90: 3.8 ± 0.8 Placebo Baseline: -1.5 ± 0.7 Day 90: -0.6 ± 0.8	No AEs reported	Turmeric extract alleviated knee pain, and improved joint function in healthy patients with chronic knee pain and was well tolerated and safe.
Singhal et al, 2021[28]	Intervention group (n=73) Paracetamol group (n=71)	40-80	500 mg twice daily of curcuminoid-essential oil complex in capsule, for 1000 mg/ day	950 mg of curcuminoids	Knee OA	42 days	WOMAC Baseline to Week 6	Intervention Baseline: 56.3 (20.5) Week 6: 43.01 ± 2.62 Paracetamol Baseline: 50.2 (19.5) Week 6: 37.93 ± 2.16	Restlessness (4.11%), tingling sensation (1.37%)	After 42 days, bioavailable turmeric extract was effective in reducing pain and other symptoms of knee OA and found to be safe.
Amalraj et al, 2017[29]	Intervention: LD group: (n= 12) HD group (n=12) Placebo group (n=12)	_	LD turmeric matrix capsule, 250 mg twice daily, 500 mg/ day HD turmeric matrix capsule, 500 mg twice daily, 1000 mg/ day	LD: 250 mg curcuminoids HD: 500 mg curcuminoids	RA	90 days	VAS and DAS28 LD turmeric group HD turmeric group Placebo	VAS Intervention LD Baseline: 7.01 ± 0.86 Postintervention: 2.63 ± 0.74 Intervention HD Baseline: 7.99 ± 0.71 Postintervention 2.21 ± 0.45 Placebo Baseline: 6.61 ± 0.73 Postintervention: 6.84 ± 0.63 DAS 28 Intervention LD Baseline: 4.51 ± 0.64 Postintervention: 2.14 ± 0.16 Intervention HD Baseline: 5.29 ± 0.54 Postintervention: 1.80 ± 0.36 Placebo Baseline: 3.53 ± 0.47 Postintervention: 3.53 ± 0.47	Mild nausea and diarrhea	After 90 days, turmeric matrix formula acted as an analgesic, anti-inflammatory agent for the management of RA and was well tolerated and without side effects.

Table 3. (continued)

Study	Sample Size	Age, y	Treatment	Curcuminoids / Curcumin Administered Daily	Indication	Duration	Scale	Mean ± SD	AE/ safety	Efficacy
Kuptniratsaikul et al, 2009[30]	Intervention group (n=52) Ibuprofen group (n=55)	50	500 mg of Curcuma domestica four times daily, 2000 mg/day	1000 mg of curcuminoids	Knee OA	42 days	Numeric scale Week 0 to Week 6	Intervention Pain on level walking: Week 0: 5.3 ± 2.3 Week 6: 2.7 ± 2.5 Pain on stairs: Week 0: 5.7 ± 2.1 Week 6: 3.1 ± 1.5 Time spent on 100-m walk (sec): Week 0: 107.9 ± 24.6 Week 6: 96.7 ±17.0 Time spent on going up and down a flight of stairs (sec): Week 0: 31.2 ± 12.6 Week 6: 24.8 ± 10.2 Ibuprofen Pain on level: Week 0: 5.0 ± 1.9 Week 6: 3.1 ± 2.3 Pain on stairs: Week 0: 6.2 ± 2.2 Week 6: 3.8 ± 2.4 Time spent on 100-m walk (sec): Week 0: 103.6 ± 22.2 Week 6: 97.0 ± 25.7 Time spent on going up and down a flight of stairs (sec) Week 0: 30.3 ± 13.8 Week 6: 25.9 ± 12.3	Dyspepsia (20.8%), dizziness (10.4%), nausea/ vomiting (6.3%), and loose stool (4.2%).	The mean scores of the outcomes at weeks 0, 2, 4, and 6 were significantly improved. *C. domestica* extracts seem to be more efficacious and safer than Ibuprofen for knee OA.
Javadi et al, 2019[31]	Intervention group (n=24) Placebo group (n=25)	_	40 mg of curcumin nanomicelle in capsule, three times daily, 120 mg/day	120 mg of curcumin, 100% encapsulation of curcumin as nanomicelles	RA	84 days	DAS28 Baseline to Postintervention	DAS28 Test Intervention Baseline 3.75 ± 1.01 Postintervention 2.87 ± 0.74 Placebo Baseline 3.45 ± 0.95 Postintervention 2.90 ± 1.02	No AEs reported	After 84 days, curcumin nanomicelles reduced the DAS-28 score significantly. Curcumin was safe and effective in management of RA
Atabaki et al, 2020[32]	Intervention group (n=15) Placebo group (n=15)	40-55	80 mg of curcumin nanomicelles once daily	80 mg of curcumin, 100% encapsulation of curcumin as nanomicelles	OA	90 days	VAS Predose, postdose	VAS Intervention Predose: 7.93 ± 0.39 Postdose: 3.4 ± 0.27 Placebo Predose 8.46 ± 0.5 Postdose 9. 1 ± 0.25	No AEs reported	After 90 days, Curcumin nanomicelles significantly reduced inflammation and pain in patients with OA.
Shep et al, 2019[33]	Intervention group (n=70) Diclofenac group (n=69)	38-65	500 mg of BCM-95 Capsule, three times daily, 1500 mg/day	1425 mg of curcuminoids	Knee OA	28 days	VAS, KOOS Baseline to day 28	VAS Intervention Baseline 7.84 ± 0.63 Day 28: 2.20 ± 0.81 Diclofenac Baseline 7.81 ± 0.73 Day 28 2.20 ± 0.61 KOOS Intervention Baseline 53.29 ± 5.70 Day 28: 88.77 ± 5.62 Diclofenac Baseline 53.15 ± 4.24 Day 28 90.38 ± 3.61	Nausea (9%), diarrhea (7%)	After 28 days, Curcumin had efficacy that was similar to diclofenac but demonstrated better tolerance among participants with knee OA. Curcumin can be alternative treatment in the patients with knee OA who are intolerant to the side effects of non-steroidal anti-inflammatory drugs.
Henrotin et al, 2019[33]	Intervention HD group (n=48) Intervention LD group (n=38) Placebo (n=40)	_	HD bio-optimized Curcuma longa extract high dose, 2x3 caps/ day, LD bio-optimized Curcuma longa extract, 2x2 caps/day plus placebo 2x1 caps/day	HD: 280.02 mg of curcumin extract LD: 186.68 mg of curcumin extract	Knee OA	90 days	VAS KOOS HD and LD	VAS Baseline Intervention HD: 62.9 (13.8) LD: 63.3 (15.8) Placebo 59.9 (12.3) EOT Intervention HD: -25.04 (26.985) LD: -28.00 (28.176) Placebo -12.25 (26.249) Change in KOOS global score T1 Baseline Intervention HD: 35.2 ± 67.5 LD: 18.0 ± 57.6 Placebo 7.9 ± 60.2 T3 Followup Intervention HD: 56.3 ± 82.6 LD: 48. ± 73.1 Placebo 42.1 ± 66.2 Change in KOOS Pain T1 Baseline Intervention HD: 7.1 ± 17.5 LD: 4.8 ± 16.7 Placebo 3.1 ± 13.9 T3 Followup Intervention HD: 12.3 ± 19.4 LD: 12.8 ± 18.4 Placebo 10.8 ± 16.5	No severe AEs; abdominal discomfort and diarrhea frequently reported AEs	At the end of 90 days, bio-optimized Curcuma longa extract was safe and well-tolerated, with no evidence of severe AEs.

Table 3. (continued)

Study	Sample Size	Age, y	Treatment	Curcuminoids / Curcumin Administered Daily	Indication	Duration	Scale	Mean ± SD	AE/ safety	Efficacy
Gupte et al, 2019[23]	Intervention group (n=17) Ibuprofen with placebo group (n=25)	40-65	400 mg of solid lipid curcumin particles twice daily, 800 mg/day	160 mg of curcumin	Knee OA	90 days	VAS, WOMAC	_	Rash and itching	Curcumin significantly decreased VAS and WOMAC scores compared to baseline from day 45 onward. SLCPs in a dose of 160 mg daily was effective and safe in alleviating symptoms of knee OA when administered for 90 days.
Nakagawa et al, 2020[25]	Intervention group (n=18) Placebo group (n=23)	40	90 mg of surface-controlled water-dispersible curcumin twice daily, 180 mg/ day, in 6 capsules daily	64.8 mg of curcuminoids.	Knee OA	180 days	JKOM, VAS, JOA, WOMAC Baseline to week 8	VAS Intervention Baseline: 0.52 8 weeks: 0.20 Placebo Baseline: 0.42 8 weeks: 0.21	No serious AEs	After 180 days, curcumin was effective in the treatment of knee OA.
Belcaro et al, 2010[35]	Test group (n=23) Control group (n=25)	40-53	1000 mg of curcumin-phosphatidyl-choline complex daily	200 mg curcumin	OA	90 days	WOMAC Baseline to 3 months postintervention	WOMAC Baseline Intervention: 83.4 Control: 80.6 After 3 months Intervention: 34.8 Control: 78.8	No AEs reported	After 90 days, complex was clinically effective in management and treatment of OA

Abbreviations: AEs, adverse events; DAS28, Disease Activity Score 28; HD, high dose; JOA, Japanese Orthopedic Association; JKOM, Japanese Knee Osteoarthritis Measure; KOOS, Knee Injury and Osteoarthritis Outcome Score; LD, low dose; OA, osteoarthritis; RA, rheumatoid arthritis; SLCPs, solid lipid curcumin particles; VAS, Visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 4. Safety and Efficacy of Combination Therapy With Turmeric Extracts and Curcumin Supplements for Joint Health Using VAS Scale

Study	Sample Size	Age, y	Treatment	Curcuminoids / Curcumin Administered Daily	Indication	Duration	Scale	Mean ± SD	AE/ safety	Efficacy
Panahi et al, 2015[36]	Intervention group (n=19) Placebo group (n=21)	<80	500 mg of curcuminoid plus 5 mg of piperine in capsules three times daily, 1500 mg/ day	1500 mg of curcuminoids	Knee OA	42 days	VAS	_	No AEs reported	After 42 days, treatment with curcumin-piperine supplementation successfully ameliorated the symptoms of knee osteoarthritis
Rahimnia et al, 2016[37]	Intervention group (n=19) Placebo group (n=21)	_	500 mg of curcuminoid plus 5 mg piperine in capsule three times daily, 1500 mg/day	1500 mg of curcuminoids	Knee OA	42 days	VAS, WOMAC, LPFI	_	No AEs reported	After 42 days, Significant improvement in clinical symptoms of OA in curcuminoid-piperine supplement treated participants cannot be attributed to the systemic anti-inflammatory effects of these phytochemicals.

Abbreviations: AEs, adverse events; OA, osteoarthritis; LPFI, lateral patellar facet impingement; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

following physical exertion. The 106 participants were randomly assigned to two groups: group 1 was administered 250 mg of a commercial, water dispersible turmeric extract, TurmXTRA 60N, in one capsule containing 150 mg curcuminoids, and group 2 received a placebo, both once daily for 90 days.

Reduction in pain intensity was measured using a VAS after an 80-m, fast-paced walk test. The turmeric extract significantly reduced the VAS score between baseline and day 90, with a greater mean reduction, 2.5 times, than that for the placebo. It also significantly decreased time taken for the 80-m, fast-paced walk test and nine-step stair-climb test, and improved all inflammatory biomarkers compared to the placebo, with a significant reduction in median TNF-α and MMP-3 compared to baseline. The study showed that the water dispersible turmeric extract significantly alleviated knee pain and improved joint function in healthy participants with chronic knee pain.

Singhal et al.[27] These researchers conducted a study to compare the efficacy and safety of a commercial, curcuminoid-essential oil complex BCM-95, Curcugreen, and paracetamol in 144 patients with knee OA. One group received 500 mg of the oil complex, containing 475 mg curcuminoids, twice daily, and the other group received 650 mg of paracetamol three times daily, for 6 weeks.

The intensity of pain and other symptoms of OA were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale.[28] After 6 weeks of treatment, most patients in the curcumin group reported improvement in WOMAC pain and function and stiffness scores. The C-reactive protein (CRP) and TNF-α levels were significantly reduced in the curcumin group.

Amalraj et al.[29] These researchers conducted a three-arm study to compare the efficacy of two doses of a commercial, complete natural turmeric matrix formulation, Acumin, with that of a placebo for patients with active RA. The 36 participants were randomly assigned to one of three groups. Twice daily for 90 days, participants received either a placebo or a low, 250-mg dose of the matrix formulation containing 125 mg of curcuminoids, or a high, 500 mg dose of the matrix formulation containing 250 mg of curcuminoids.

Participants' responses were assessed using the American College of Rheumatology (ACR) criteria response,30 a VAS, the Disease Activity Score 28 (DAS28),[31] and CRP levels. Both matrix formulations demonstrated significant anti-inflammatory and analgesic properties by improving the erythrocyte sedimentation rate (ESR), CRP, VAS, rheumatoid factor (RF), DAS28, and ACR responses relative to the baseline. The high dose curcumin group showed greater reductions in the DAS and VAS scores.

Kuptniratsaikul et al.[32] These researchers conducted RCT to determine the efficacy and safety of Curcuma domestica (C. Domestica) extracts for pain reduction and functional improvement in patients with knee OA. The 107 patients with primary knee OA who had pain scores of greater than or equal to 5 of 10 on a numerical rating scale were randomly divided into two groups. They received either 500 mg of the C. Domestica extract, containing 250 mg of curcuminoids, four times daily, or 800 mg of ibuprofen daily for 6 weeks.

Pain intensity was assessed using a numerical rating scale, and knee function was assessed by the time spent on a 100-m walk and going up and down a flight of stairs with 10 steps. All parameters showed decreasing trends in both groups. No significant difference existed in the scores among patients receiving ibuprofen or *C. domestica*.

Javadi et al.[33] These researchers conducted a randomized, double-blind, controlled study to determine the effects of commercial curcumin nanomicelles, SinaCurcumin, on the clinical symptoms of patients with RA. The 65 patients were divided into two groups, with one to receive 40 mg of curcumin nanomicelles in a capsule and the other a placebo capsule, both three times daily for 12 weeks.

Disease activity was measured using the DAS28 after 12 weeks, which showed a reduction in both groups. However, the difference between the two groups wasn't significant.

Atabaki et al.[34] These researchers conducted a double-blind, randomized, placebo-controlled study to assess the effects of commercial curcumin nanomicelles, SinaCurcumin, on the immune responses of patients with OA. The 30 patients were equally divided into two groups: one group received 80 mg of curcumin nanomicelles, and the other group received a placebo, both once a day for 3 months. In addition, all participants received 50 mg of diclofenac sodium.

The intervention group had decreased scores on a VAS; decreased levels of CRP, CD4+, CD8+ T cells, and Th17 cells; and decreased B-cell frequency, demonstrating a significant reduction in inflammation and pain in patients with OA.

Shep et al.[35] These researchers conducted a randomized, open-label, parallel, active-controlled study in patients with knee OA to compare the efficacy and safety of a commercial, curcuminoid-essential oil complex, BCM-95, with that of diclofenac. The study included 139 patients who were randomly assigned to receive either 500 mg of the oil complex, containing 475 mg curcuminoids, in a capsule three times daily or a 50-mg tablet of diclofenac twice daily for 28 days.

Pain was evaluated using the VAS and the Knee Injury and Osteoarthritis Outcome Score (KOOS).[36] Patients who received curcumin showed a improvement in the KOOS score and pain severity that was similar to that of diclofenac.

Henrotin et al.[37] These researchers conducted a randomized, double-blind, placebo-controlled study to compare the efficacy of two doses of a commercial, bio-optimized Curcuma longa extract (BCL), Flexofytol, which contains 46.67 mg of turmeric rhizome extract, for symptomatic knee OA. 150 patients with knee OA in the study were followed up for 90 days. Patients were randomly assigned to one of three groups, receiving either three placebo capsules twice a day, a low dose of curcumin in two capsules plus one capsule of placebo twice a day, or a high dose of curcumin in 3 capsules twice a day.

Pain intensity was assessed using VAS and KOOS Scores. Pain reduction at day 90 in the low- and high-dose BCL groups, at -29.5 mm and -36.5 mm, respectively, was higher than that in the placebo group. The KOOS global score and subscales were significantly improved over time in all the groups ($P<.001$), and no significant differences existed between the groups. Significantly more AEs occurred in the high-dose curcumin group than in the low-dose curcumin and placebo groups.

Gupte et al.[38] These researchers performed a randomized, placebo-controlled study to evaluate the efficacy and safety of commercial, solid lipid curcumin particles (SLCP), Longvida, in 42 patients with knee OA. The patients were randomly assigned to receive 400 mg in an SLCP capsule containing 80 mg of curcumin twice daily or 400 mg of ibuprofen in a placebo capsule once daily, for 90 days.

Knee pain and function were assessed using WOMAC and a VAS. Curcumin significantly decreased the VAS and WOMAC scores compared to baseline from day 45 onward. This effect was comparable to that of the low-dose ibuprofen used in the study.

Nakagawa et al.[39] These researchers performed an open-label, noncomparative study to evaluate the efficacy and safety of a commercial, surface-controlled water-dispersible curcumin, Theracurmin, in knee OA. The 50 patients were randomly assigned to receive 90 mg of curcumin, containing 32.4 mg curcuminoids, or a placebo, both twice daily in 6 capsules daily for 6 months.

Knee symptoms were measured using the Japanese Knee Osteoarthritis Measure (JKOM)[40] and the knee scoring system of the Japanese Orthopedic Association (JOA).[41] A knee pain VAS is included in the JKOM. The VAS, JKOM, and JOA scores at 6 months after treatment were significantly better than those at baseline.

Belcaro et al.[42] These researchers conducted a three-month pilot study to assess the efficacy and safety of a commercial curcumin-phosphatidylcholine complex, Meriva, in 50 patients with OA. Participants in Group A were assigned to receive either the best available treatment as defined by a patient's physician; and Group B was managed using the best available treatment plus 1000 mg of a curcumin-phosphatidylcholine complex containing 200 mg curcumin, daily for 3 months.

The WOMAC score was used to assess pain intensity. At the end of treatment, the reduction in the WOMAC score in the curcumin group was significantly greater than that in the control group.

Panahi et al.[43] These researchers conducted a randomized, double-blind, placebo-controlled study to investigate the efficacy of a curcuminoid-piperine supplement, C3 Curcumin Complex, in reducing the systemic oxidative burden in patients with knee OA. The 40 patients with mild-to-moderate, primary knee OA were randomly divided into two groups, with one group receiving 500 mg of curcuminoids plus 5 mg of piperine (Bioperine) in a capsule three times daily or matched placebo capsules, for 6 weeks.

A significant improvement was observed in the systemic oxidative stress biomarkers after 6 weeks of curcuminoid-piperine supplementation. A significant elevation in serum superoxide dismutase (SOD) activity and in glutathione (GSH) concentrations occurred as well as a significant reduction in malondialdehyde (MDA) concentrations in the curcuminoid-piperine group compared to the placebo group.

Rahimnia et al.[44] These researchers performed a randomized, double-blind, placebo-controlled, parallel group study to determine effects of a curcuminoid-piperine supplementation, the C3 complex, on inflammatory biomarkers in 40 patients with OA. Patients were randomly allocated to receive either 500 mg of curcuminoids plus 5 mg of piperine (Bioperine) in a capsule or a placebo, three times daily for 6 weeks.

Serum levels of inflammatory biomarkers, such as IL-4, IL-6, TNF-α, transforming growth factor-β (TGF-β), and HS-CRP, together with ESR, were determined at baseline and at the end of the trial. A comparison of the magnitude of the changes in the evaluated inflammatory biomarkers indicated no significant differences between the groups.

Joint Health: Meta-analysis

Participants aged 18 to 80 years were treated with either a monotherapy, a turmeric extract standardized for curcuminoids, or a combination of a curcuminoids and a pharmacological treatment. Pain intensity was assessed using VAS, WOMAC, DAS28, JKOM, JOA, KOOS, a numerical rating scale, and ACR, and Lequesne's Pain Functional Index (LPFI). The studies for both monotherapy and the combination therapies concluded that curcumin was effective in reducing pain intensity and improving joint function, with no major or severe AEs.

Table 5. Efficacy of Turmeric Extracts and Curcumin Supplements in Joint Health Using Random Effects Model

Product Comparison	Mean Difference	Standard Error	95% CI	Weightage %
Intervention vs Comparator				
Amalraj et al[24]				
Low-dose turmeric matrix formulation and placebo	-4.21	0.28	[-4.79, -3.63]	17.33
High-dose turmeric matrix formulation and placebo	-4.63	0.22	[-5.09, -4.17]	17.36
Average	0	0	[-4.86, -4.05]	
Shep et al[33]				
Curcuminoid essential oil complex and Diclofenac	0	0.12	[-0.24, 0.24]	17.39
Average	0	0	[-0.24, 0.24]	
Atabaki et al[32]				
Curcumin nanomicelles and placebo	-5.70	0.10	[-5.89: -5.51]	17.39
Average	0	0	[-5.89: -5.51]	
Thanawala et al[27]				
Water dispersible turmeric extract and placebo	4.40	0.16	[4.09, 4.71]	17.38
Average	0	0	[4.09, 4.71]	
Henrotin et al[33]				
High-dose bio-optimized Curcuma longa extract and placebo	13.15	5.43	[2.36, 23.94]	7.17
Low-dose bio-optimized Curcuma longa extract and placebo	15.75	6.28	[3.23, 28.27]	5.98
Average	0	0	[6.21, 22.32]	
Combined				
Average	0.12	1.90	[-3.59, 3.85]	

Results

The heterogeneity analysis found a χ^2 value for Cochran's Q statistic of 3666.80 and $P < .0001$, which showed that statistical heterogeneity existed among the studies; therefore, the random effects model was used. The χ^2 value of the random effects model was 1400.65, with $P < .0001$, which was statistically significant. Table 5 shows that the difference between the intervention and control groups was statistically significant [SMD 0.12 (-3.59; 3.85), $P < .00001$].

The research team analyzed data for five RCTs for patients with RA, OA, chronic knee pain, or knee OA. The studies used treatments: (1) of a low dose of turmeric matrix formulation, (2) a high dose of a turmeric matrix formulation, (3) a curcuminoid essential oil complex, (4) curcumin nanomicelles, (5) a water dispersible turmeric extract, (6) a high dose of bio-optimized Curcuma longa extract, and (7) a low dose of bio-optimized Curcuma longa extract. The VAS score was considered to be an efficacy parameter.

Significant differences existed between groups: (1) between the low-dose turmeric matrix formulation and the placebo [SMD -4.21 (-4.79, -3.63)], (2) between the high-dose turmeric matrix formulation and the placebo [SMD -4.63 (-5.09, -4.17), (1) & (2) combined $P < .00001$], (3) between the curcumin nanomicelles and the placebo [SMD -5.70 (-5.89, -5.51), $P < .00001$], (4) between the water dispersible turmeric extract and the placebo [SMD -1 (-1.25, 0.75), $P < .00001$], (5) between the high-dose bio-optimized Curcuma longa extract and the placebo [SMD 13.15 (2.36, 23.94)], and (6) between the low-dose bio-optimized Curcuma longa extract and the placebo with [SMD 15.75 (3.23, 28.27), (5) & (6) combined $P < .00001$].

Figure 3 shows the forest plot for each study on a single plot. The size of the plot symbols is proportional to the sample size of the study. The points on the plot are sorted by study and mean difference. The lines represent the confidence intervals for the mean differences. A narrow confidence interval indicates a greater degree of precision.

The heterogeneity analysis had a χ^2 value for Cochran's Q statistic of 372.6017, with $P < .0001$, which showed that statistical heterogeneity existed among the studies; therefore, the random effects model was used. The χ^2 value of the random effects model was 48.0968 ($P < .0001$), which was statistically significant. Table 6 shows that the difference between the intervention and control groups was statistically significant [SMD -0.76 (-1.86, 0.337], $P < .00001$].

Statistically significant differences existed between groups: (1) between the water dispersible turmeric extract and the low-dose bio-optimized Curcuma longa extract [SMD -24.20 (-31.87, -16.53), (2) between the curcuminoid-essential oil complex and the high-dose bio-optimized Curcuma longa extract [SMD -23.20 (-29.58, -16.82), and (3) between the water dispersible turmeric extract and the high-dose bio-optimized Curcuma longa extract [SMD -21.60 (-28.95, -14.25).

Figure 4 shows a forest plot that presents the results of each study on a single plot. It shows that the studies with no significant differences tentatively fell on the plot's vertical line. Those comparisons were: (1) the water dispersible turmeric extract and the curcuminoid-essential oil complex [SMD 1.60 (1.31, 1.89)], (2) between the curcumin nanomicelles and the curcuminoid-essential oil complex [SMD 1.20 (0.78, 1.62)], (3) between the water dispersible turmeric extract and the low-dose turmeric matrix formulation [SMD 1.17 (0.67, 1.67)], and (4) between the high-dose turmeric matrix formulation and the curcumin nanomicelles [SMD -1.19 (-1.48, -0.90)].

On Figure 4, the size of the plot symbols is proportional to the sample size of the study. The points on the plot are sorted by study and mean difference. The lines represent the confidence intervals for the mean differences. A narrow confidence interval indicates a greater degree of precision.

OBSERVATIONS ON SAFETY

In most studies, very few AEs or no severe AEs occurred with turmeric extract and curcumin supplements, showing that it's well tolerated globally. The most reported AEs in the evaluated trials were dyspepsia,[34] dizziness,[29] nausea, [38,26,34] vomiting,[34] abdominal discomfort,[26] diarrhea,[26,34,38,39] rash, itching,[37] tingling sensation, and restlessness,[32] all which were reported to be self-limiting.

None of the patients required rescue medication for AE management. Overall, the benefits of Curcuma longa extract and curcumin supplementation were significantly greater than their risks. Therefore, it can be recommended for musculoskeletal conditions.

Figure 3. Forest plot showing efficacy of curcumin supplements in joint health

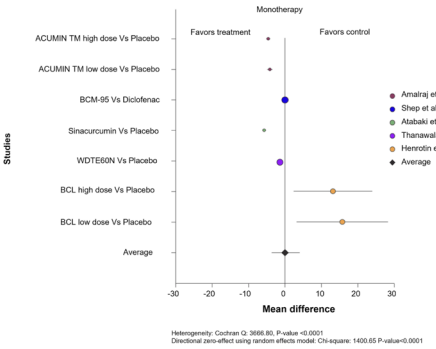
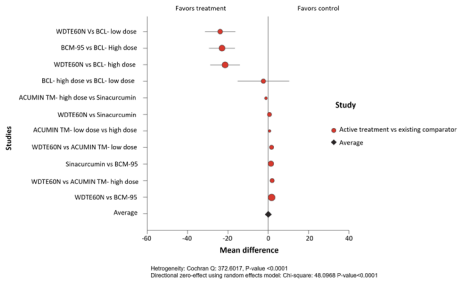


Table 6. Efficacy of Curcumin Supplements Using Random Effects Model.

Product Comparison	Mean Difference	Standard Error	95% CI	Weightage
Intervention vs Comparator				
Water dispersible turmeric extract and low-dose Curcuma longa extract	-24.20	3.8547	[-31.87, -16.53]	1.8195
Curcuminoid-essential oil complex and high-dose Curcuma longa extract	-23.20	3.2211	[-29.58, -16.82]	2.4628
Water dispersible turmeric extract and high-dose Curcuma longa extract	-21.60	3.7065	[-28.95, -14.25]	1.9466
High-dose and low-dose bio-optimized Curcuma longa extract	-2.60	6.3876	[-15.32, 10.12]	0.7245
High-dose turmeric matrix formulation and curcumin nanomicelles	-1.19	0.1396	[-1.48, -0.90]	13.4372
Water dispersible turmeric extract and curcumin nanomicelles	0.40	0.2108	[-0.02, 0.82]	13.2944
Low Dose and high dose turmeric matrix formulation	0.42	0.2500	[-0.10, 0.94]	13.1929
Water dispersible turmeric extract and low-dose turmeric matrix formulation	1.17	0.2525	[0.67, 1.67]	13.1860
Curcumin nanomicelles and curcuminoid essential oil complex	1.20	0.2125	[0.78, 1.62]	13.2904
Water dispersible turmeric extract and high-dose turmeric matrix formulation	1.59	0.2400	[1.11, 2.07]	13.2204
Water dispersible turmeric extract and curcuminoid essential oil complex	1.60	0.1467	[1.31, 1.89]	13.4254
Combined				
Average	-0.76	0.5588	[-1.86, 0.337]	

Figure 4. Forest plot showing efficacy of various curcumin supplements



DISCUSSION

The current meta-analysis has demonstrated the effectiveness of curcumin in skeletal muscle health. Several studies in the current review demonstrated that turmeric extract and curcumin can effectively reduce postexercise pain, inflammation, oxidative stress, and muscle soreness. Thanawala et al[20] conducted a study and reported that the intake of 250 mg of water dispersible turmeric extract before

and after eccentric exercise could significantly reduce the subjective perception of muscle soreness.

Mallard et al,[19] Jager et al,[22] Drobnic et al,[10] Tanabe et al,[23] and Amalraj et al[24] demonstrated the effectiveness of curcumin in reducing postexercise pain, modulating inflammatory pathways, reducing lactate accumulation in an exercising population, attenuating damage from oxidative stress and inflammation related to acute muscle injury, and reducing DOMS without major side effects. Wang et al[25] demonstrated that nanobubble water curcumin extract (NCE) has the potential to reduce the risk of musculoskeletal injury.

The current meta-analysis has demonstrated the effectiveness of curcumin in improving joint health. Several studies have reported that curcumin is safe and effective for various joint health conditions, such as joint pain, OA, and RA. Thanawala et al[26] demonstrated that a dose of 250 mg of water dispersible turmeric extract can substantially alleviate knee pain and improve joint function in healthy participants without any AEs. Singhal et al[27] reported a significant improvement in WOMAC scores in knee OA patients, whereas Shep D et al[35] reported a nonsignificant improvement in the KOOS scores of patients with knee OA, using a bioavailable turmeric extract. Atabaki et al,[34] Panahi et al,[43] Belcaro et al,[42] and Rahimnia et al[44] demonstrated that curcumin at doses of up to 1500 mg/day was effective and significantly reduced inflammation, systemic oxidative burden, and pain without any AEs in patients with OA.

Amalraj et al,[29] at doses of 250 mg and 500 mg, and Javadi et al,[33] at a dose of 120 mg or 40 mg three times a day evaluated the efficacy of curcumin in relieving the symptoms of RA and reported the safety and efficacy of curcumin in patients with RA. Henrotin et al[37] and Nakagawa Yet al[39] demonstrated that curcumin is safe and effective for management of knee OA.

Based on the current literature review of randomized clinical studies, the research team observes that most of the turmeric extract formulations contained approximately 20-40% curcuminoids, whereas the water dispersible turmeric extract, WDTE60N, contained 60% natural curcuminoids. In the randomized, double-blind, placebo controlled, clinical trials for joint health and DOMS, the water dispersible turmeric extract showed clinical benefits at the same single daily dose of 250 mg, 150 mg of curcuminoids, as compared to placebo.[20,26]

CONCLUSIONS

Turmeric extract and curcumin supplements can be effective adjuvants for the management of musculoskeletal health, with a low incidence of AEs. The water-dispersible turmeric extract, WDTE60N, at a dose of 250 mg per day was found to be more effective than some curcumin products. However, the studies included in the analysis were conducted using diverse doses and treatment durations. Further evaluation using comparisons in future clinical trials can establish the appropriate effective dose of curcumin supplements for the overall maintenance of musculoskeletal health.

AUTHORS' DISCLOSURE STATEMENT

Lynda Doyle is an employee of Avant Nutrition; Prabakaran Desomayanandam and Arun Bhuvanendran are employees of In vitro Research Solutions (iVRS); Somepalli Venkateswarlu and Surendra Bachu are employees of Laila Nutraceuticals; and Shefali Thanawala and Rajat Shah are employees of Nutriventia. The authors don't have any other conflicts of interest to declare related to the meta-analysis.

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