



March 27, 2023

Re: Revive: Curated Blend and Cellular Absorption Technology Clinical Dossier

Here at THREE, we provide curated proactive wellness solutions using our proprietary Cellular Absorption Technology, proven to help you live a life of greater health and purpose.

This dossier contains peer-reviewed clinical studies both on the curated blend and the Cellular Absorption Technologies used in Revive that validates its ability to do the following:

- Support healthy joints.
- Ease muscle stiffness.
- Maintain a healthy inflammatory status in the body.
- Promote exercise recovery.
- Counteract the effect of free radicals.

One thing that you can expect from us here at THREE is that we are always in the process of running clinical studies in elucidating new mechanisms of action by which our products work along with discovering additional areas in which our products can promote human health. We have several exciting clinical studies in the pipeline and will announce these when they are completed.

The clinical studies contained herein, and others that will follow, explain why our products provide the powerful health benefits our customers from all around the world experience every time they use a THREE product.

Thank you for joining us on this journey and for trusting us with your proactive wellness needs.

Be well,

Dr. Dan Gubler  
Chief Scientific Officer  
Three International



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Review Crit Rev Food Sci Nutr. 2007;47(8):735-48. doi: 10.1080/10408390601062054.

# Black pepper and its pungent principle-piperine: a review of diverse physiological effects

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Affiliations

PMID: 17987447 DOI: [10.1080/10408390601062054](https://doi.org/10.1080/10408390601062054)

## Abstract

Black pepper (*Piper nigrum*) is one of the most widely used among spices. It is valued for its distinct biting quality attributed to the alkaloid, piperine. Black pepper is used not only in human dietaries but also for a variety of other purposes such as medicinal, as a preservative, and in perfumery. Many physiological effects of black pepper, its extracts, or its major active principle, piperine, have been reported in recent decades. Dietary piperine, by favorably stimulating the digestive enzymes of pancreas, enhances the digestive capacity and significantly reduces the gastrointestinal food transit time. Piperine has been demonstrated in in vitro studies to protect against oxidative damage by inhibiting or quenching free radicals and reactive oxygen species. Black pepper or piperine treatment has also been evidenced to lower lipid peroxidation in vivo and beneficially influence cellular thiol status, antioxidant molecules and antioxidant enzymes in a number of experimental situations of oxidative stress. The most far-reaching attribute of piperine has been its inhibitory influence on enzymatic drug biotransforming reactions in the liver. It strongly inhibits hepatic and intestinal aryl hydrocarbon hydroxylase and UDP-glucuronyl transferase. Piperine has been documented to enhance the bioavailability of a number of therapeutic drugs as well as phytochemicals by this very property. Piperine's bioavailability enhancing property is also partly attributed to increased absorption as a result of its effect on the ultrastructure of intestinal brush border. Although initially there were a few controversial reports regarding its safety as a food additive, such evidence has been questionable, and later studies have established the safety of black pepper or its active principle, piperine, in several animal studies. Piperine, while it is non-genotoxic, has in fact been found to possess anti-mutagenic and anti-tumor influences.

## Related information

[BioSystems](#)[PubChem Compound \(MeSH Keyword\)](#)

## LinkOut - more resources

[Full Text Sources](#)[Taylor & Francis](#)



FULL TEXT LINKS

Randomized Controlled Trial [Phytother Res.](#) 2019 May;33(5):1457-1468.

doi: 10.1002/ptr.6338. Epub 2019 Mar 6.

# A pilot, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of a novel *Boswellia serrata* extract in the management of osteoarthritis of the knee

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Affiliations

PMID: 30838706 PMID: [PMC6681146](#) DOI: [10.1002/ptr.6338](#)[Free PMC article](#)

## Abstract

A double-blind, placebo-controlled human trial was conducted to evaluate the safety and efficacy of a standardized oral supplementation of Boswellin®, a novel extract of *Boswellia serrata* extract (BSE) containing 3-acetyl-11-keto- $\beta$ -boswellic acid (AKBBA) with  $\beta$ -boswellic acid (BBA). A total of 48 patients with osteoarthritis (OA) of the knee were randomized and allocated to the BSE and placebo groups for intervention. Patients were administered BSE or placebo for a period of 120 days. The trial results revealed that BSE treatment significantly improved the physical function of the patients by reducing pain and stiffness compared with placebo. Radiographic assessments showed improved knee joint gap and reduced osteophytes (spur) confirming the efficacy of BSE treatment. BSE also significantly reduced the serum levels of high-sensitive C-reactive protein, a potential inflammatory marker associated with OA of the knee. No serious adverse events were reported. This is the first study with BSE conducted for a period of 120 days, longer than any other previous clinical trial on patients with OA of the knee. The findings provide evidence that biologically active constituents of BSE, namely, AKBBA and BBA, act synergistically to exert anti-inflammatory/anti-arthritis activity showing improvement in physical and functional ability and reducing the pain and stiffness.

**Keywords:** *Boswellia serrata* extract; anti-inflammatory; cathepsin G; high-sensitive C-reactive protein; knee osteoarthritis; microsomal prostaglandin E synthase-1.

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## Figures



FULL TEXT LINKS

Meta-Analysis [BMC Complement Med Ther.](#) 2020 Jul 17;20(1):225.

doi: 10.1186/s12906-020-02985-6.

# Effectiveness of Boswellia and Boswellia extract for osteoarthritis patients: a systematic review and meta-analysis

Ganpeng Yu <sup>1</sup>, Wang Xiang <sup>2 3</sup>, Tianqing Zhang <sup>4 5</sup>, Liuting Zeng <sup>6</sup>, Kailin Yang <sup>7</sup>, Jun Li <sup>8</sup>

Affiliations

PMID: 32680575 PMID: [PMC7368679](#) DOI: [10.1186/s12906-020-02985-6](#)[Free PMC article](#)

## Abstract

**Background:** Osteoarthritis (OA) is the commonest form of inflammatory joint disease. Unfortunately, to date, there is no appropriate treatment for OA. Boswellia serrata was considered as a potent anti-inflammatory, anti-arthritic and analgesic agent that may be a drug for OA.

**Methods:** In this meta-analysis, data from randomized controlled trials were obtained to assess the effects of Boswellia or its extract versus placebo or western medicine in patients with OA. The primary outcomes included visual analogue score (VAS), WOMAC pain, WOMAC stiffness, WOMAC function and lequesne index.

**Result:** Seven trials involving 545 patients were included. Compared with the control group, Boswellia and its extract may relieve the pain [VAS: (WMD -8.33; 95% CI -11.19, - 5.46; P<0.00001); WOMAC pain: (WMD -14.22; 95% CI -22.34, - 6.09; P = 0. 0006)] and stiffness [WOMAC stiffness: (WMD -10.04; 95% CI -15.86, - 4.22; P = 0. 0007)], and improve the joint's function [WOMAC function: (WMD -10.75; 95% CI -15.06, - 6.43; P<0. 00001); lequesne index: (WMD -2.27; 95% CI -3.08, - 1.45; P<0. 00001)].

**Conclusion:** Based on current evidence, Boswellia and its extract may be an effective and safe treatment option for patient with OA, and the recommended duration of treatment with Boswellia and its extract is at least 4 weeks.

**Keywords:** Boswellia; Boswellia extract; Meta-analysis; Osteoarthritis; Systematic review.

## Figures



## FULL TEXT LINKS



[Drug Deliv.](#) 2010 Nov;17(8):587-95. doi: 10.3109/10717544.2010.501461.

## Complexation with phosphatidyl choline as a strategy for absorption enhancement of boswellic acid

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## Affiliations

PMID: 20624027 DOI: [10.3109/10717544.2010.501461](#)

### Abstract

Boswellic acids (BAs) are isolated from oleo gum resin of *Boswellia serrata* and are reported to be effective as anti-inflammatory, hypolipidemic, immunomodulatory, and anti-tumor. Pharmacokinetic studies of boswellic acid reveal its poor absorption through the intestine. The objective of the present study is to enhance bioavailability of boswellic acid by its complexation with phosphatidylcholine. A complex of boswellic acid was prepared with phosphatidylcholine and characterized on the basis of solubility, melting point, TLC, and IR. An everted intestine sac technique was used to study ex-vivo drug absorption of boswellic acid-phosphatidylcholine (BA-PC) complex and plain boswellic acid. Anti-inflammatory activity of the complex was compared with boswellic acid in carrageenan-induced paw edema in rats. Hypolipidemic activity was also evaluated in Triton-induced hyperlipidemia. The complex was also converted into vesicles (phytosomes) and compared with other vesicular systems (liposomes and niosomes) by evaluating its anti-inflammatory effect. Analytical reports along with spectroscopic data revealed the formation of a complex. The results of ex-vivo study show that BA-PC complex has significantly increased absorption compared with boswellic acid, when given in equimolar doses. The complex showed better anti-inflammatory and hypolipidemic activity as compared to BA. Among all vesicular systems phytosomes showed maximum anti-inflammatory activity. Enhanced bioavailability of the BA-PC complex may be due to the amphiphilic nature of the complex, which greatly enhance the water and lipid solubility of the boswellic acid. The present study clearly indicates the superiority of complex over boswellic acid, in terms of better absorption, enhanced bioavailability and improved pharmacokinetics.

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Meta-Analysis    [Semin Arthritis Rheum.](#) 2018 Dec;48(3):416-429.

doi: 10.1016/j.semarthrit.2018.03.001. Epub 2018 Mar 10.

## Efficacy of curcumin and Boswellia for knee osteoarthritis: Systematic review and meta-analysis

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Affiliations

PMID: 29622343    PMCID: [PMC6131088](#)    DOI: [10.1016/j.semarthrit.2018.03.001](#)

[Free PMC article](#)

### Abstract

**Purpose:** The unfavorable safety profiles of commonly prescribed knee osteoarthritis (OA) treatments have led clinicians and patients to seek safer alternatives. Research has suggested that curcuminoid and boswellia formulations could moderate key inflammatory pathways that are associated with worsening symptoms and disease progression. We conducted a systematic review and meta-analysis to assess the efficacy and safety of these treatments vs. placebo or NSAIDs for knee OA.

**Methods:** We searched Medline, EMBASE, Google Scholar, Web of Science and the Cochrane database from inception to February 21, 2018. We also hand searched reference lists and reviewed conference proceedings. We included randomized clinical trials (RCTs) comparing curcuminoid or boswellia formulations with placebo or NSAIDs for knee OA. We calculated standardized mean differences (SMD) or risk ratios (RR) for all relevant outcomes. Meta-analyses were conducted using random effects models. Heterogeneity was assessed using the  $I^2$  statistic.

**Results:** Eleven RCTs (N = 1009) were eligible for analysis. Study quality was low overall, and most included RCTs were conducted on fewer than 100 participants. Both curcuminoid and boswellia formulations were statistically significantly more effective than placebo for pain relief and functional improvement. There were no significant differences between curcuminoids or boswellia and placebo in safety outcomes. Curcuminoids showed no statistically significant differences in efficacy outcomes compared to NSAIDs; patients receiving curcuminoids were significantly less likely to experience gastrointestinal adverse events. No RCTs compared boswellia against approved NSAIDs.

**Conclusions:** The results of our study suggest that curcuminoid and boswellia formulations could be a valuable addition to the knee OA treatment regimens by relieving symptoms while reducing safety risks. The current body of evidence is not adequate in size or quality to make any meaningful clinical practice recommendations. Further research through large, high quality RCTs probably investigating the synergistic effect of these products with other OA treatments is warranted.

## FULL TEXT LINKS



Review [Phytother Res.](#) 2022 Jul;36(7):2767-2778. doi: 10.1002/ptr.7477. Epub 2022 May 16.

# The effect of curcumin supplementation on delayed-onset muscle soreness, inflammation, muscle strength, and joint flexibility: A systematic review and dose-response meta-analysis of randomized controlled trials

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## Affiliations

PMID: 35574627 DOI: [10.1002/ptr.7477](#)

## Abstract

To quantify the effects of curcumin supplementation on exercise-induced muscle damage, muscle soreness, inflammatory biomarkers, muscle strength, and joint flexibility via assessment of creatine kinase (CK), visual analogue scale (VAS) score, maximal voluntary contraction (MVC), and range of motion (ROM), respectively. Online databases, including PubMed, Google Scholar, and Scopus, were searched up to February 2021. RevMan® software (version 5.3) was used for assessing the risk of bias to assess the quality of studies. The mean differences (MD) and confidence intervals (95% CI) of CK activity (IU/L), VAS score, tumor necrosis factor (TNF- $\alpha$ ) (pg/ml), interleukin-6 (IL-6) (pg/ml), IL-8 (pg/ml), MVC (nm) and ROM (degree) were pooled using a random- or fixed-effect model. Between-study heterogeneity was assessed using  $\chi$ -square or  $I^2$  statistic. Ten trials met the eligibility criteria and were included in the pooled analysis. Meta-analysis showed that curcumin supplementation significantly reduced serum CK activity [WMD = -65.98 IU/L, 95% CI (-99.53 to -32.44)], muscle soreness [WMD = -0.56, 95% CI (-0.84 to -0.27)], and TNF- $\alpha$  concentration [WMD = -0.22 pg/ml, 95% CI (-0.33 to -0.10)]. Also, curcumin supplementation elicited significant improvements in MVC [WMD = 3.10 nm, 95% CI (1.45-4.75)] and ROM [WMD = 6.49°, 95% CI (3.91-9.07)], although no significant changes in IL-6 and IL-8 levels were found. Dose-response analysis indicated that there is a significant non-linear association between the daily dose and the final effect size regarding TNF- $\alpha$ . Curcumin supplementation may improve some aspects of DOMS, including muscle damage, muscle soreness, inflammation, muscle strength, and joint flexibility. Further, well-designed and high-quality studies with larger sample sizes are needed to ascertain the long-term effects and safety of curcumin supplementation.

**Keywords:** creatine kinase; curcumin; meta-analysis; muscle damage; muscle soreness.

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## Related information

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[Meta-Analysis](#) [Phytother Res.](#) 2021 Apr;35(4):1768-1781. doi: 10.1002/ptr.6912.

Epub 2020 Nov 10.

# The effect of curcumin supplementation on recovery following exercise-induced muscle damage and delayed-onset muscle soreness: A systematic review and meta-analysis of randomized controlled trials

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Affiliations

PMID: 33174301 DOI: [10.1002/ptr.6912](#)

## Abstract

**Background:** curcumin consumption may have a protective effect against exercise-induced muscle damage (EIMD) through stabilization of the cell membrane via inhibition of free radical formation. Evidence supporting a protective role of curcumin after physical activity induced muscle injury in humans, however, it is inconsistent.

**Methods:** Medline, Scopus, and Google scholar were systematically searched up to May 2020. The Cochrane Collaboration tool for assessing the risk of bias was used for assessing the quality of studies. Random effects model, weighted mean difference (WMD), and 95% confidence interval (CI) were used for estimating the overall effect. Between-study heterogeneity was assessed using the chi-squared and  $I^2$  statistic.

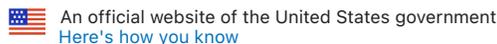
**Results:** The results revealed a significant effect of curcumin supplementation on reducing creatine kinase (CK) (weighted mean difference [WMD] =  $-48.54 \text{ IU.L}^{-1}$ ; 95% CI:  $-80.667, -16.420$ ;  $p = .003$ ) and muscle soreness index decrease (WMD =  $-0.476$ ; 95% CI:  $-0.750, -0.202$ ;  $p = .001$ ). Moreover, a subgroup analysis resulted in a significant decrease in CK concentrations and muscle soreness index, according to follow-ups after exercise, dose of curcumin, duration of studies, exercise type, train status and study design.

**Conclusions:** The current evidence revealed a efficacy of curcumin in reducing CK serum levels and muscle soreness index among adults. Therefore, curcumin may be known as a priority EIMD recovery agent in interventions.

**Keywords:** creatine kinase; curcumin; meta-analysis; muscle damage; muscle soreness; systematic review.

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Review J Affect Disord. 2021 Jan 1;278:627-636. doi: 10.1016/j.jad.2020.09.091.

Epub 2020 Sep 29.

# The effect of oral curcumin supplementation on health-related quality of life: A systematic review and meta-analysis of randomized controlled trials

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Affiliations

PMID: 33038707 DOI: [10.1016/j.jad.2020.09.091](https://doi.org/10.1016/j.jad.2020.09.091)

## Abstract

**Background and aims:** With an aging society, a multitude of physical, mental, and emotional challenges are being faced both in the general population and by those with chronic disorders. An enhanced understanding of 'quality of life' could be considered a major criterion for improved clinical care. We performed a meta-analysis to examine the effect of oral curcumin on improving the health-related quality of life (HRQOL).

**Methods:** A systematic search was performed through PubMed, Clarivate Web of Science, Scopus, and Embase up to February 2020 using relevant keywords. Trials that met the inclusion criteria were included in this study. We applied the standardized mean difference (SMD) in a random-effects model to analyze the impact of combined trials. Additionally, we used the Cochrane Risk Bias Tool to evaluate any potential risks of bias.

**Results:** A total of 10 studies were considered eligible and included in the meta-analysis. We found an overall significant effect of oral curcumin supplementation on improved HRQOL (SMD: 2.46, 95% CI: 1.30, 3.63; I<sup>2</sup>=97.4). In the subgroup analysis, curcumin showed significantly favorable effects on HRQOL in trials with a short duration of curcumin intervention (<5 months) and those that used curcumin formulations with high bioavailability.

**Conclusion:** Oral curcumin has a strong positive impact on HRQOL. Our analysis supports the use of an improved-bioavailability formulation of curcumin to improve HRQOL. However, given the heterogeneity among the studies included in this review, additional evidence from well-designed, large, and long-term trials is still required.

**Keywords:** Curcumin; Meta-analysis; Quality of life.

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## Related information

FULL TEXT LINKS

Review [Phytother Res.](#) 2022 Dec;36(12):4361-4370. doi: 10.1002/ptr.7642.

Epub 2022 Oct 7.

# The effects of curcumin-containing supplements on inflammatory biomarkers in hemodialysis patients: A systematic review and meta-analysis

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Affiliations

PMID: 36205586 DOI: [10.1002/ptr.7642](#)

## Abstract

In the past decade, the effect of curcumin or turmeric supplementation on many aspects of health status in different populations has been evaluated. In the present study, a systematic review and meta-analysis were conducted to estimate the effect of curcumin administration on inflammatory markers in hemodialysis (HD) patients. A systematic search was performed in MEDLINE, EMBASE, Scopus, and Clarivate Analytics Web of Science databases from 1997 until June 2022 for terms related to curcumin/turmeric and hemodialysis (HD). Randomized, double-blind/single-blind studies examining the effects of curcumin/turmeric on the inflammation of HD participants older than 18 years were considered eligible for inclusion. Data were pooled using the weighted mean difference (WMD) and 95% CI as the summary statistic, considering a random-effects analysis model. The data that were pooled from nine studies with 472 patients indicated that curcumin-containing supplement had significant effect on serum C-reactive protein (CRP) levels (WMD = -3.3 mg/L; 95% CI: -5.4 to -1.3;  $p < 0.001$ ,  $I^2 = 76.7\%$ , 8 studies, 467 participants), and interleukin-6 (IL-6) levels (SMD: -0.4; 95% CI: -0.8 to -0.07;  $p = 0.02$ ,  $I^2 = 31.6\%$ , 3 studies, 153 participants) compared control group. Although curcumin intervention could not change tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) concentration (SMD = -0.3; 95% CI: -0.7 to 0.04;  $p = 0.08$ ,  $I^2 = 25.3\%$ , 3 studies, 153 participants), when compared with the placebo group. Our study's main limitations were small number of studies, overall high risk of bias in the included trials, and high heterogeneity in some results. The present meta-analysis suggested that intervention with curcumin-containing supplements was associated with a significant reduction in serum hs-CRP and IL-6 concentrations in HD patients. The curcumin intervention in the reduction of hs-CRP levels was greater than the minimal clinically important difference (MCID) for CRP (0.5 mg/L), which can be helpful in physicians' clinical decisions.

**Keywords:** curcumin; cytokines; hemodialysis patients; inflammation; systematic reviews and meta-analysis; turmeric.

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Meta-Analysis    Biosci Rep. 2021 Jun 25;41(6):BSR20210817. doi: 10.1042/BSR20210817.

# The efficacy and safety of Curcuma longa extract and curcumin supplements on osteoarthritis: a systematic review and meta-analysis

Liuting Zeng # <sup>1</sup>, Ganpeng Yu # <sup>2</sup>, Wensa Hao <sup>3</sup>, Kailin Yang # <sup>4</sup>, Hua Chen <sup>1</sup>

Affiliations

PMID: 34017975    PMCID: [PMC8202067](#)    DOI: [10.1042/BSR20210817](#)[Free PMC article](#)

## Abstract

**Objective:** To assess the efficacy and safety of Curcuma longa extract and curcumin supplements on osteoarthritis (OA).

**Methods:** The databases such as Pubmed and Cochrane Library were searched to collect the article about Curcuma longa extract and curcumin in the treatment of OA. Then, randomized controlled trials (RCTs) were selected and their data were extracted. Finally, the RevMan5.3 was utilized for risk of bias assessment and meta-analysis, the STATA15.0 were utilized for publication bias assessment, and GRADE tool were used for the evidence quality assessment of primary outcomes.

**Results:** A total of 15 RCTs involving 1621 participants were included. (1) Compared with placebo, Curcuma longa extract and curcumin (C.) can decrease the visual analog scale (VAS) and The Western Ontario and McMaster Universities (WOMAC) score-pain, the WOMAC score-function and the WOMAC score-stiffness. In terms of adverse events, Curcuma longa extract and curcumin are comparable with those of placebo. (2) Compared with non-steroidal anti-inflammatory drugs (NSAIDs), Curcuma longa extract and curcumin have similar effects on joint pain, function and stiffness. The incidence of adverse events in Curcuma longa extract and curcumin was lower. (3) Compared with the NSAIDs group, C.+NSAIDs can also decrease the VAS and WOMAC score-pain, the WOMAC score-function and the WOMAC score-stiffness. In terms of adverse events, the addition of Curcuma longa extract and curcumin to NSAIDs did not increase adverse events.

**Conclusion:** Curcuma longa extract and curcumin may be a safer and effective supplement for OA patients. It is recommended to use Curcuma longa extract and curcumin supplement for OA patients for more than 12 weeks.

**Keywords:** Curcuma longa Extract; Curcumin; Meta-analysis; Osteoarthritis; Systematic review.

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FULL TEXT LINKS

Review [Complement Ther Med](#). 2021 Dec;63:102775. doi: 10.1016/j.ctim.2021.102775.

Epub 2021 Sep 16.

# The efficacy of high- and low-dose curcumin in knee osteoarthritis: A systematic review and meta-analysis

An-Fang Hsiao <sup>1</sup>, Yi-Chieh Lien <sup>2</sup>, I-Shiang Tzeng <sup>3</sup>, Chien-Ting Liu <sup>4</sup>, Sheng-Hsun Chou <sup>5</sup>, Yi-Shiung Horng <sup>6</sup>

Affiliations

PMID: 34537344 DOI: [10.1016/j.ctim.2021.102775](#)[Free article](#)

## Abstract

**Objectives:** The aim of this study was to critically appraise and evaluate effects of low- and high-dose curcuminoids on pain and functional improvement in patients with knee osteoarthritis (OA) and to compare adverse events (AEs) between curcuminoids and non-steroid anti-inflammatory drugs (NSAIDs).

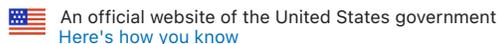
**Methods:** We systematically reviewed all randomized controlled trials (RCTs) on curcuminoids in knee osteoarthritis from the PubMed, Embase, Cochrane Library, AMED, Cinahl, ISI Web of Science, Chinese medical database, and Indian Scientific databases from inception to June 21, 2021.

**Results:** We included eleven studies with a total of 1258 participants with primary knee OA. The meta-analysis results showed that curcuminoids were significantly more effective than comparators regarding visual analogue scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores. However, no significant difference in pain relief or AEs between the high-dose (daily dose  $\geq 1000$  mg or total dose  $\geq 42$  gm) and low-dose (daily dose  $< 1000$  mg or total dose  $< 42$  gm) curcuminoid treatments was observed. When comparing curcuminoids versus NSAIDs, a significant difference in VAS pain was found. For AE analysis, three of our included studies used NSAIDs as comparators, with all reporting higher AE rates in the NSAID group, though significance was reached in only one study.

**Conclusions:** The results of our meta-analysis suggest that low- and high-dose curcuminoids have similar pain relief effects and AEs in knee OA. Curcuminoids are also associated with better pain relief than NSAIDs; therefore, using curcuminoids as an adjunctive treatment in knee OA is recommended.

**Keywords:** Clinical trial; Curcumin; Curcuminoid; Knee osteoarthritis; Meta-analysis; Systematic review.

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FULL TEXT LINKS



[J Agric Food Chem](#). 2018 Nov 21;66(46):12421-12430. doi: 10.1021/acs.jafc.8b04136.

Epub 2018 Nov 8.

# Fabrication and Characterization of Curcumin-Loaded Liposomes Formed from Sunflower Lecithin: Impact of Composition and Environmental Stress

Shengfeng Peng <sup>1</sup>, Liqiang Zou <sup>1</sup>, Wei Liu <sup>1</sup>, Chengmei Liu <sup>1</sup>, David Julian McClements <sup>2</sup>

Affiliations

PMID: 30372060 DOI: [10.1021/acs.jafc.8b04136](https://doi.org/10.1021/acs.jafc.8b04136)

## Abstract

There is significant interest in the formulation of liposome-based delivery systems using cheap plant-based commercial sources of lecithin. This study evaluated the impact of phospholipid type on the formation, stability, and curcumin-loading of sunflower liposomes. Four kinds of sunflower lecithin (Sunlipon 50, 65, 75, and 90) with different phosphatidylcholine (PC) levels were used to prepare the liposomes using microfluidization. The particle size, surface charge, microstructure, and stability of the liposomes were determined. All four kinds of lecithin were suitable for fabricating stable liposomes regardless of the PC content. Curcumin was loaded into the liposomes using a newly developed pH-driven method. The loading capacity and heat stability of curcumin increased as the PC content of the lecithin increased. These results showed that commercial plant-based lecithins may be suitable for overcoming some of the hurdles normally associated with using liposomes in the food industry, such as high cost and poor stability.

**Keywords:** curcumin; delivery; liposomes; pH-driven method; sunflower lecithin.

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Meta-Analysis [Front Immunol.](#) 2022 Jul 22;13:891822. doi: 10.3389/fimmu.2022.891822.  
eCollection 2022.

# Efficacy and Safety of Curcumin and *Curcuma longa* Extract in the Treatment of Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trial

[Liuting Zeng](#)<sup>1</sup>, [Tiejun Yang](#)<sup>2</sup>, [Kailin Yang](#)<sup>3</sup>, [Ganpeng Yu](#)<sup>2</sup>, [Jun Li](#)<sup>2, 3</sup>, [Wang Xiang](#)<sup>4</sup>, [Hua Chen](#)<sup>1</sup>

## Affiliations

PMID: 35935936 PMID: [PMC9353077](#) DOI: [10.3389/fimmu.2022.891822](#)

[Free PMC article](#)

## Abstract

**Background:** Modern pharmacological research found that the chemical components of *Curcuma longa L.* are mainly curcumin and turmeric volatile oil. Several recent randomized controlled trials (RCT) have shown that curcumin improves symptoms and inflammation in patients with arthritis.

**Methods:** Pubmed, Cochran Library, CNKI, and other databases were searched to collect the randomized controlled trials (RCTs). Then, the risk of bias of RCTs were assessed and data of RCTs were extracted. Finally, RevMan 5.3 was utilized for meta-analysis.

**Results:** Twenty-nine (29) RCTs involving 2396 participants and 5 types of arthritis were included. The arthritis included Ankylosing Spondylitis (AS), Rheumatoid Arthritis (RA), Osteoarthritis (OA), Juvenile idiopathic arthritis (JIA) and gout/hyperuricemia. Curcumin and Curcuma longa Extract were administered in doses ranging from 120 mg to 1500 mg for a duration of 4–36 weeks. In general, Curcumin and Curcuma longa Extract showed safety in all studies and improved the severity of inflammation and pain levels in these arthritis patients. However, more RCTs are needed in the future to elucidate the effect of Curcumin and Curcuma longa Extract supplementation in patients with arthritis, including RA, OA, AS and JIA.

**Conclusion:** Curcumin and Curcuma longa Extract may improve symptoms and inflammation levels in people with arthritis. However, due to the low quality and small quantity of RCTs, the conclusions need to be interpreted carefully.

**Keywords:** Curcuma longa extract; ankylosing spondylitis; curcumin; juvenile idiopathic arthritis; meta-analysis; osteoarthritis; rheumatoid arthritis; systematic review.

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Review Cytokine. 2023 Apr;164:156144. doi: 10.1016/j.cyto.2023.156144. Epub 2023 Feb 15.

# Antioxidant and anti-inflammatory effects of curcumin/turmeric supplementation in adults: A GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials

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## Abstract

Turmeric and its prominent bioactive compound, curcumin, have been the subject of many investigations with regard to their impact on inflammatory and oxidative balance in the body. In this systematic review and meta-analysis, we summarized the existing literature on randomized controlled trials (RCTs) which examined this hypothesis. Major databases (PubMed, Scopus, Web of Science, Cochrane Library and Google Scholar) were searched from inception up to October 2022. Relevant studies meeting our eligibility criteria were obtained. Main outcomes included inflammatory markers (i.e. C-reactive protein(CRP), tumour necrosis factor $\alpha$ (TNF- $\alpha$ ), interleukin-6(IL-6), and interleukin 1 beta(IL-1 $\beta$ )) and markers of oxidative stress (i.e. total antioxidant capacity (TAC), malondialdehyde(MDA), and superoxide dismutase (SOD) activity). Weighted mean differences (WMDs) were reported. P-values < 0.05 were considered significant. Sixty-six RCTs were included in the final analysis. We observed that turmeric/curcumin supplementation significantly reduces levels of inflammatory markers, including CRP (WMD: -0.58 mg/l, 95 % CI: -0.74, -0.41), TNF- $\alpha$  (WMD: -3.48 pg/ml, 95 % CI: -4.38, -2.58), and IL-6 (WMD: -1.31 pg/ml, 95 % CI: -1.58, -0.67); except for IL-1 $\beta$  (WMD: -0.46 pg/ml, 95 % CI: -1.18, 0.27) for which no significant change was found. Also, turmeric/curcumin supplementation significantly improved anti-oxidant activity through enhancing TAC (WMD = 0.21 mmol/l; 95 % CI: 0.08, 0.33), reducing MDA levels (WMD = -0.33  $\mu$ mol/l; 95 % CI: -0.53, -0.12), and SOD activity (WMD = 20.51 u/l; 95 % CI: 7.35, 33.67). It seems that turmeric/curcumin supplementation might be used as a viable intervention for improving inflammatory/oxidative status of individuals.

**Keywords:** Antioxidant status; Curcumin; Inflammation markers; Meta-analysis; Turmeric.

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Meta-Analysis    *Nutr Rev.* 2021 Aug 9;79(9):1043-1066. doi: 10.1093/nutrit/nuaa114.

# Anti-inflammatory effects of oral supplementation with curcumin: a systematic review and meta-analysis of randomized controlled trials

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PMID: 34378053    DOI: [10.1093/nutrit/nuaa114](https://doi.org/10.1093/nutrit/nuaa114)

## Abstract

**Context:** Chronic inflammation is a major contributor to the development of noncommunicable diseases. Curcumin, a bioactive polyphenol from turmeric, is a well-known anti-inflammatory agent in preclinical research. Clinical evidence remains inconclusive because of discrepancies regarding optimal dosage, duration, and formulation of curcumin.

**Objective:** The aim of this systematic review, conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and checklist, was to evaluate the efficacy of curcumin supplementation on systemic inflammatory mediators, comparing dose, duration, and bioavailability status of interventions.

**Data sources:** The Medline, CINAHL, EMBASE, Scopus, and Cochrane literature databases were searched from 1980 to May-end 2019. Randomized controlled trials investigating effects of dietary curcumin on inflammatory mediators in humans not receiving anti-inflammatory treatment were eligible for inclusion. Two authors independently assessed titles and abstracts of identified articles for potential eligibility and respective, retrieved, full-text articles; disagreements were resolved by a third author. Evidence quality was critically appraised using the Quality Criteria Checklist for Primary Research.

**Data extraction:** Thirty-two trials (N = 2,038 participants) were included and 28 were meta-analyzed using a random-effects model; effect sizes were expressed as Hedges' g (95%CI).

**Data analysis:** Pooled data (reported here as weighted mean difference [WMD]; 95%CI) showed a reduction in C-reactive protein (-1.55 mg/L; -1.81 to -1.30), interleukin-6 (-1.69 pg/mL, -2.56 to -0.82), tumor necrosis factor  $\alpha$  (-3.13 pg/mL; -4.62 to -1.64), IL-8 (-0.54 pg/mL; -0.82 to -0.28), monocyte chemoattractant protein-1 (-2.48 pg/mL; -3.96 to -1.00), and an increase in IL-10 (0.49 pg/mL; 0.10 to 0.88), with no effect on intracellular adhesion molecule-1.

**Conclusion:** These findings provide evidence for the anti-inflammatory effects of curcumin and support further investigation to confirm dose, duration, and formulation to optimize anti-inflammatory effects in humans with chronic inflammation.

**Systematic review registration:** PROSPERO registration no. CRD42019148682.

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Review [Phytother Res.](#) 2023 Mar;37(3):1212-1224. doi: 10.1002/ptr.7730. Epub 2023 Jan 17.

# A systematic review and meta-analysis of randomized controlled trials investigating the effect of the curcumin and piperine combination on lipid profile in patients with metabolic syndrome and related disorders

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## Abstract

Metabolic syndrome is characterized by multiple metabolic disorders. Several studies indicated that curcumin plus piperine could affect lipids profiles in various diseases. The present meta-analysis aims to assess the effect of curcumin plus piperine on lipid profiles in patients with MetS and associated disorders using a systematic review and meta-analysis of randomized controlled trials. Trials were searched by several electronic databases up to May 2022. The Comprehensive Meta-Analysis (CMA) version3 software carried out this systematic review and meta-analysis. Random-effects model and the inverse variance method were used to conduct the meta-analysis. We evaluated the publication bias and heterogeneity of all eligible studies. In addition, subgroup analyses and sensitivity assessments were performed to assess potential sources of heterogeneity. The combined results by the random-effects model demonstrated that curcumin plus piperine significantly decreased total cholesterol and LDL-C in patients suffering from metabolic syndrome. In comparison, the results of the overall effect size did not show any significant change in triglyceride concentrations. Our results were robust in sensitivity analysis and were not dependent on the dose of curcumin, the dose of piperine, and the duration of treatment. Our results showed that co-administration of piperine and curcumin supplementation improves the lipid profile in metabolic syndrome. However, further long-term RCTs are required to ascertain their clinical benefit.

**Keywords:** curcumin; lipid profile; metabolic syndrome; piperine.

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[J Agric Food Chem](#). 2018 Nov 21;66(46):12421-12430. doi: 10.1021/acs.jafc.8b04136.

Epub 2018 Nov 8.

# Fabrication and Characterization of Curcumin-Loaded Liposomes Formed from Sunflower Lecithin: Impact of Composition and Environmental Stress

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PMID: 30372060 DOI: [10.1021/acs.jafc.8b04136](https://doi.org/10.1021/acs.jafc.8b04136)

## Abstract

There is significant interest in the formulation of liposome-based delivery systems using cheap plant-based commercial sources of lecithin. This study evaluated the impact of phospholipid type on the formation, stability, and curcumin-loading of sunflower liposomes. Four kinds of sunflower lecithin (Sunlipon 50, 65, 75, and 90) with different phosphatidylcholine (PC) levels were used to prepare the liposomes using microfluidization. The particle size, surface charge, microstructure, and stability of the liposomes were determined. All four kinds of lecithin were suitable for fabricating stable liposomes regardless of the PC content. Curcumin was loaded into the liposomes using a newly developed pH-driven method. The loading capacity and heat stability of curcumin increased as the PC content of the lecithin increased. These results showed that commercial plant-based lecithins may be suitable for overcoming some of the hurdles normally associated with using liposomes in the food industry, such as high cost and poor stability.

**Keywords:** curcumin; delivery; liposomes; pH-driven method; sunflower lecithin.

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[Randomized Controlled Trial](#) [Complement Ther Clin Pract.](#) 2022 Nov;49:101666.

doi: 10.1016/j.ctcp.2022.101666. Epub 2022 Sep 17.

# Efficacy and safety of oral Nigella sativa oil for symptomatic treatment of knee osteoarthritis: A double-blind, randomized, placebo-controlled clinical trial

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Affiliations

PMID: 36150238 DOI: [10.1016/j.ctcp.2022.101666](#)

## Abstract

**Background and purpose:** The oil of Nigella sativa (NS) seeds has analgesic and anti-inflammatory effects. Therefore, the efficacy and safety of NS oil in the treatment of knee osteoarthritis were evaluated.

**Materials and methods:** One hundred and sixteen patients aged 50-70 years were randomly assigned to take 2.5 mL NS oil (N = 58) or placebo (N = 58) orally every 8 h for 1 month. WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) was the primary outcome measure and Visual Analog Scale (VAS) for pain, number of 500 mg acetaminophen tablets taken per day during the trial, patients' satisfaction with the interventions, complete blood count and the blood levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine and blood urea nitrogen were the secondary outcome measures.

**Results:** Fifty two and 54 patients respectively in the NS oil and placebo groups completed the study. The VAS scores were decreased by  $33.96 \pm 17.04\%$  (NS oil group) and  $9.21 \pm 0.32\%$  (placebo group) ( $p < 0.001$ ), and WOMAC total scores were decreased by  $27.72 \pm 18.61\%$  (NS oil group) and  $1.34 \pm 2.31\%$  (placebo group) ( $p < 0.001$ ) compared to baseline. The NS oil reduced the dose of acetaminophen significantly compared with the placebo ( $p = 0.001$ ). The patients were significantly more satisfied with the NS oil than the placebo ( $p < 0.001$ ). The NS oil had no significant effect on the other variables. There was no side effect.

**Conclusion:** Oral NS oil safely reduces the osteoarthritis symptoms and analgesic dose in the knee osteoarthritis patients.

**Keywords:** Black seed; Complementary medicine; Nigella sativa; Osteoarthritis; Traditional Persian medicine.

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[Review](#) [Phytomedicine](#). 2018 Jul 15;46:69-77. doi: 10.1016/j.phymed.2018.04.018.

Epub 2018 Apr 10.

# Nigella sativa fixed oil as alternative treatment in management of pain in arthritis rheumatoid

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Affiliations

PMID: 30097124 DOI: [10.1016/j.phymed.2018.04.018](#)

## Abstract

**Background:** N. sativa seeds is the source of fixed oil, which contain fatty acids and thymoquinone. N. sativa fixed oil topically or orally is used traditionally for management of pain in back, joints, musculoskeletal organs and arthritis rheumatoid.

**Purpose:** The aim of this review article was to evaluate the potential effects of N. sativa fixed oil in pain and inflammation, especially in arthritis rheumatoid.

**Methods:** All information was extracted from accessible and inaccessible sources (books, electronic sources, thesis and etc.).

**Results:** The results of our investigation showed N. sativa fixed oil, especially thymoquinone content had valuable anti-inflammatory and analgesic effects via different pathways. The efficacy of thymoquinone as potential treatment was confirmed in different animal model of arthritis and the clinical studies confirmed the oral (n = 4) and topical use (n = 1) of N. sativa fixed oil without adverse effects in patients suffering from arthritis rheumatoid.

**Conclusion:** The larger multicenter clinical trials for comparing the efficacy of topical, oral administrations and current treatment may help to understand better the efficacy of valuable fixed oil.

**Keywords:** Arthritis rheumatoid; Fixed oil; Inflammation; Nigella sativa; Pain; Thymoquinone.

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*Mol Immunol.* 2021 Jul;135:21-27. doi: 10.1016/j.molimm.2021.03.015. Epub 2021 Apr 12.

# Thymoquinone, extract from *Nigella sativa* seeds, protects human skin keratinocytes against UVA-irradiated oxidative stress, inflammation and mitochondrial dysfunction

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PMID: 33857815 DOI: [10.1016/j.molimm.2021.03.015](https://doi.org/10.1016/j.molimm.2021.03.015)

## Abstract

Ultraviolet A (UVA) irradiation caused skin keratinocytes to accumulate reactive oxygen species (ROS) leading to the skin injury. Thymoquinone (TQ) was identified as the prominent bioactive ingredient in *Nigella sativa* seeds which was applied in therapying various human diseases. This study aimed to illustrate the role and mechanism of TQ in UVA-induced skin injury. We pre-treated HaCaT cells with TQ and irradiated them by UVA. MTT and Elisa assays were used to evaluate cell viability and apoptosis, as well as cytokine levels. To detect the related parameters of oxidative stress and mitochondrial function, colorimetry, spectrophotometry, bioluminescence, and dual-luciferase reporter methods were used. RT-qPCR and western blotting were performed for expressions of related mRNAs and proteins. TQ significantly improved the UVA-induced cytotoxicity on HaCaT cells. TQ treatment alleviated the oxidative stress and inflammation in UVA-irradiated keratinocytes. Besides, UVA irradiation promoted mitochondrial dysregulation in HaCaT cells leading to cell apoptosis, which could be reversed by TQ treatment. More importantly, NrF2/ARE pathway was activated in TQ-treated cells, while COX-2 was depressed, and inhibiting the pathway or activating COX-2 blocked the therapeutic effect of TQ on UVA-induced skin cell injury. Our study suggested that TQ treatment attenuated the UVA-induced oxidative and inflammatory responses, as well as mitochondrial apoptosis in keratinocytes by COX-2 inhibition via activating NrF2/ARE pathway. This might be a novel sight for preventing the solar radiation damage to the skin.

**Keywords:** Inflammation; Mitochondrial dysfunction; Oxidative stress; Thymoquinone; UVA.

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Review [Biomed Pharmacother.](#) 2022 Oct;154:113559. doi: 10.1016/j.biopha.2022.113559.  
Epub 2022 Aug 19.

# Peppermint essential oil: its phytochemistry, biological activity, pharmacological effect and application

Hui Zhao <sup>1</sup>, Shan Ren <sup>2</sup>, Han Yang <sup>2</sup>, Shun Tang <sup>2</sup>, Chenyang Guo <sup>3</sup>, Maolun Liu <sup>2</sup>, Qiu Tao <sup>2</sup>, Tianqi Ming <sup>2</sup>, Haibo Xu <sup>4</sup>

Affiliations

PMID: 35994817 DOI: [10.1016/j.biopha.2022.113559](#)

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## Abstract

*Mentha* (also known as peppermint), a genus of plants in the taxonomic family Lamiaceae (mint family), is widely distributed throughout temperate regions of the world. *Mentha* contains various constituents that are classified as peppermint essential oil (PEO) and non-essential components. PEO, consisting mainly of menthol, menthone, neomenthol and iso-menthone, is a mixture of volatile metabolites with anti-inflammatory, antibacterial, antiviral, scolicidal, immunomodulatory, antitumor, neuroprotective, antifatigue and antioxidant activities. Mounting evidence indicates that PEO may pharmacologically protect gastrointestinal, liver, kidney, skin, respiratory, brain and nervous systems, and exert hypoglycemic and hypolipidemic effects. Clinically, PEO is used for gastrointestinal and dermatological diseases, postoperative adjuvant therapy and other fields. This review aims to address the advances in the extraction and isolation of PEO, its biological activities, pharmacological effects, toxicity and applications, with an emphasis on the efficacy of PEO on burn wounds and psoriasis, providing a comprehensive foundation for research, development and application of PEO in future.

**Keywords:** Application; Biological activity; *Mentha*; Pharmacological effect; Phytochemistry; peppermint essential oil.

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Review [Annu Rev Food Sci Technol](#). 2019 Mar 25;10:43-73.

doi: 10.1146/annurev-food-032818-122010. Epub 2019 Jan 21.

# Quillaja Saponin Characteristics and Functional Properties

[Corina L Reichert](#)<sup>1</sup>, [Hanna Salminen](#)<sup>1</sup>, [Jochen Weiss](#)<sup>1</sup>

Affiliations

PMID: 30664381 DOI: [10.1146/annurev-food-032818-122010](https://doi.org/10.1146/annurev-food-032818-122010)

## Abstract

Consumer concerns about synthetically derived food additives have increased current research efforts to find naturally occurring alternatives. This review focuses on a group of natural surfactants, the Quillaja saponins, that can be extracted from the Quillaja saponaria Molina tree. Quillaja saponins are triterpenoid saponins comprising a hydrophobic quillaic acid backbone and hydrophilic sugar moieties. Commercially available Quillaja saponin products and their composition and properties are described, and the technofunctionality of Quillaja saponins in a variety of food, cosmetic, and pharmaceutical product applications is discussed. These applications make use of the biological and interfacial activities of Quillaja saponins and their ability to form and stabilize colloidal structures such as emulsions, foams, crystallized lipid particles, heteroaggregates, and micelles. Further emphasis is given to the complexation and functional properties of Quillaja saponins with other cosurfactants to create mixed surfactant systems, an approach that has the potential to facilitate new interfacial structures and novel functionalities.

**Keywords:** saponins; colloidal properties; complexation; interfacial behavior; technofunctionality.

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