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Bioactive Curcumin and its Effects on Lowering Systemic Inflammation as Measured by CRP: A Systematic Review

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Abstract

Objectives: The purpose of this study was to analyze and evaluate evidence supporting curcumin lowering the systemic inflammatory marker, CRP in humans. **Methods:** A systematic literature search was completed using PubMed and MEDLINE databases. Results: After inclusion and exclusion criteria, 9 studies were evaluated, and the percent change of CRP blood levels was calculated and analyzed. **Results:** The results for these studies show strong statistical significance for the C3 complex with Bioperine and nano curcumin. Bioactive curcumin exhibits a higher percent decrease of blood level CRP than trials using only curcumin or turmeric. **Conclusion:** Overall bioactive curcumin/ curcumin with Bioperine are alternative treatments for lowering the systemic inflammation marker, CRP.

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ABSTRACT
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Keywords: curcumin, bioactive curcumin, curcuminoids, systemic inflammation, CRP, hs-CRP, C - reactive protein

INTRODUCTION

Curcumin (Curcuma longa) is the major bioactive component of the rhizomatous herbaceous perennial plant turmeric, a widely used spice in Indian and Chinese medicine and widely consumed in the Asian diet.[1,2] Curcumin (1,7-bis-4-hydroxy-3-methoxyphenyl0-1,6-heptadiene-3,5-dione) also known as diferuloylmethane, is the primary polyphenol found in turmeric.[2] Curcuma longa has been traditionally used in Asian countries as a medicinal and therapeutic herb for its antioxidant and anti-inflammatory properties.[3] Curcumin has been shown to modulate multiple signaling molecules and demonstrates activity at the cellular level which supports its multiple health benefits for inflammatory conditions.[4,5] Even with its reported benefits, a major problem with ingesting curcumin has been its poor bioavailability.[6] Several additives have been tested to improve curcumins bioavailability, one of which is piperine, the major active component of black pepper. Piperine has been associated with 2000% increase in bioavailability for curcumin.[6,7] When formulated with biodegradable nano particles by emulsion technique, the curcumin is then entrapped in the particles and has demonstrated a 9 fold increase in oral bioavailability when compared to piperine.[8]

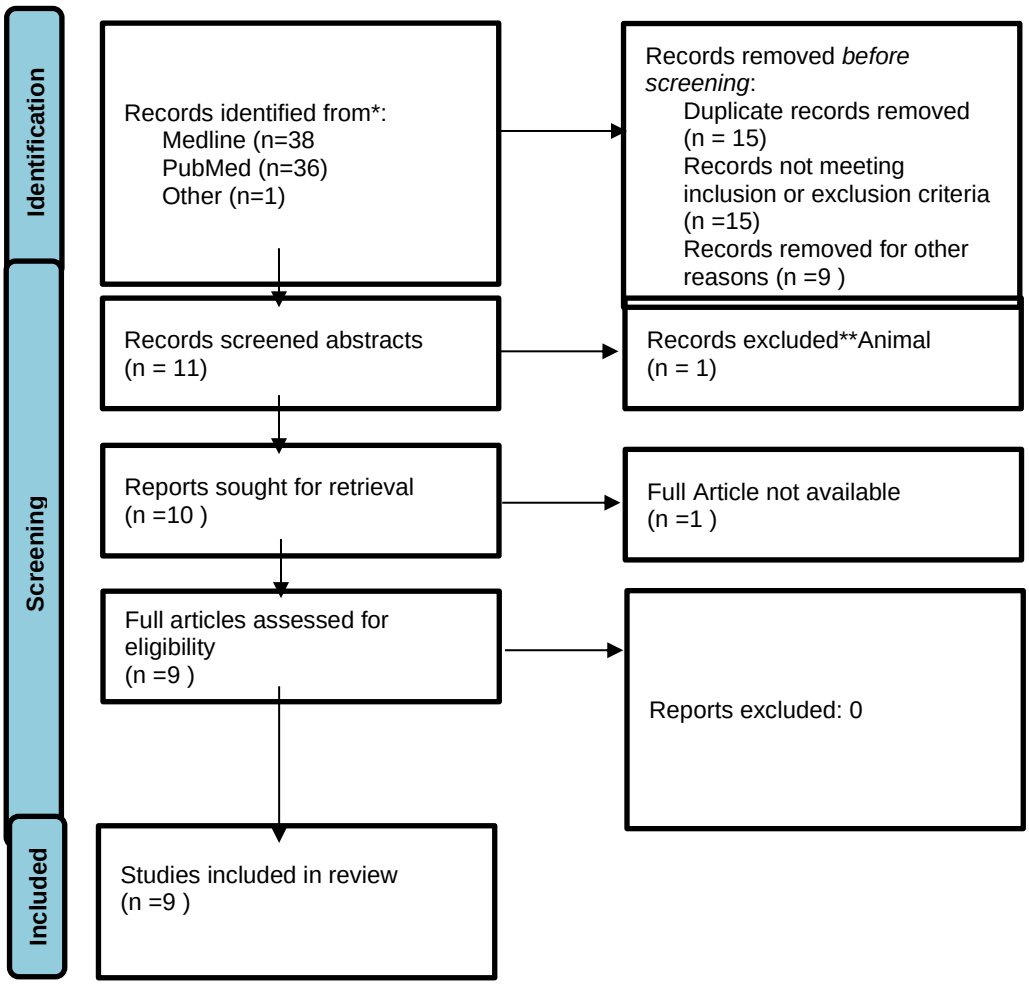
CRP/Systemic Inflammation

C - reactive protein (CRP) is a polypeptide molecule of the pentrxains family and is normally synthesized primarily by the liver in response to specific pro-inflammatory cytokines, especially interleukin-6 (IL-6). CRP is the primary marker of inflammation and a protein of acute systemic inflammation and has been long been recognized as a useful marker for inflammatory conditions like cardiovascular disease, Rheumatoid arthritis, and infection.[9-12] Serum CRP levels can change rapidly from 10 -100 fold within 6-72 hours of an inflammatory event. CRP is not the only biomarker for inflammation status but is the most commonly used and is an inexpensive method for evaluation.[13-15] The elevated levels correlate to the onset and the extent of the inflammation response. [16] The blood of healthy individuals has scarce amounts of CRP and rise robustly during tissue damage or inflammation associated with trauma, infection/non-infectious diseases. It has been wrongly concluded that the biological actions of CRP are only manifested when blood levels are elevated. It has been shown that CRP is an important mediator of biological activities such as in the absence of blood elevation.[17] The aim of this systematic review is to examine studies of the effect of curcumin, nano-particle curcumin, and curcumin with bioperine on lowering the systemic inflammatory marker, CRP in humans.

METHODS

This systematic review was done following Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines and was conducted by an independent researcher. Two databases were searched, PubMed and Medline on 9-30-21. The following Medical Subject Headings (MeSH) were used: curcumin, bioactive curcumin, curcuminoids systemic inflammation, CRP, hs-CRP, C - reactive protein. Full text articles were reviewed for inclusion and exclusion criteria. (See figure 1)

This review included any human research studies with participants aged 18 to 80 years. Only randomized control studies were included. Non-primary research was excluded and clinical trials and randomized control trials (RCT) on curcumin and effects on CRP and systemic inflammation were used. For the interest of bioavailability trials on nano-curcumin, curcumin and bioperine/ curcumin were included. In each clinical trial or RCT percent change of blood level CRP was calculated and P-values for each outcome group were reported (see table 1). The Bias assessment tool used was the Cochrane risk-of-bias tool for randomized trials.



**Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).*
***If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.*

Figure 1. 2020 Flow Diagram for New Systematic Reviews Which Included Searches of Databases and Registers Only

RESULTS

Study selection & Study Characteristics

A total of 75 articles were found, 36 from PubMed, 38 from Medline and 1 from other sources. After duplicate removal and excluding non-primary research, 15 remained, after excluding animal trials, 14 remained. The trials that measured CRP, C - reactive protein and hs-CRP were included, leaving 9 trials. (See table 1).

Table 1. Characteristics of Selected Trials Included in this Review

Author/ year	Type of curcumin	Length of intervention	number of participants	Age range of participants	Dosage of curcumin	Type of trial
Alvarenga, 2020	Orange, carrot, curcumin juice	12 weeks	28	18 and older	2.5 g turmeric (95% curcuminoids) Control group received juice without curcumin	Pilot randomized double blind controlled study
Rodrigues, 2021	curcuminoid	12 weeks	43	20-75	1 g capsules (standardized dry extract 96.84% curcuminoids) Placebo group received corn starch capsules	Randomized double blind placebo-controlled trial
Afshar, 2020	Nano curcumin	12 weeks	60	18-80	120 mg nano-curcumin Placebo group received paraffin soft gel capsules	Parallel randomized controlled clinical trial
Kocher, 2016	Curcumin Demethoxycurcumin Bis-demethoxycurcumin	6 weeks	32	17 men(50 +- 20) 25 women(52 +- 20)	241.2 mg curcumin,47.1 mg DMC, 5.9 mg BDMC(294.2 mg curcuminoids) placebo received 80.4 mg curcumin, 15.6 mg DMC, 2.0 mg BDMC	Randomized double blind crossover trial
Rahimnia, 2015	Curcuminoids/piperine	6 weeks	40	5732 +- 8.78 57.57 +- 9.05	1500 mg curcumin/15 mg piperine	Randomized double blind placebo controlled trial
Panahi, 2015	C3 complex-Curcumin/Bioperine	4 weeks	89	Groups were matched in age	500 mg curcumin/5 mg Bioperine	Randomized double blind placebo controlled pilot study
Panahi, 2012	C3 complex-curcumin/ Bioperine	4 weeks	96	37-59	1 g	Randomized double blind placebo controlled clinical trial
Samadian, 2017	Turmeric/ curcumin	12 weeks	71	18 and older	500 mg Tumeric/ 22.1 mg curcumin	Double blind placebo controlled randomized clinical trial
Helli, 2020	Curcumin/ nano curcumin	8 weeks	90	40-80	Group 1: 500 mg curcumin Group 2: 80mg nano curcumin Group 3: placebo	Random control trial

A total of 549 subjects were enrolled among the 9 included trials. The subjects were human adults and included males and females with an age range of 18-80. The participants in each trial were being evaluated for inflammation being caused by, chronic kidney disease[18-21] cardiovascular disease[22,23] sulfur mustard intoxication,[24,25] or osteoarthritis.[26] The curcumin, nano-curcumin, and curcumin/bioperine dosages ranged from 80.4 mg-2.5g. Of the studies included, all were randomized trials and incorporated blinding and placebo groups. Two out of the 9 trials had participants with high CRP levels which equates to 10 mg/L and above (see table 2).[17,20,24]

Table 2. CRP P-values/ percent change

Author/Year	Percent change CRP Values curcumin group	Percent change CRP Values placebo group
Alvarenga, 2020	-47.36	+13.79
Rodrigues, 2021	+7.69	-5.17
Afshar, 2020	-46.71	-3.47
Kocher,2016	0	-5.5
Rahimnia, 2015	-4.13	+4.4
Panahi, 2015	-34.09	-7.25
Panahi, 2012	-43.41	-9.48
Samadian, 2017	-37.09	+42.85
Helli, 2020	Curcumin nano -42.56 -46.8	-0.79

Quality of Assessment and Risk of Bias

The risk of bias for the studies reviewed was assessed and it was found that there is a low bias across trials. Potential issues with bias for some of the trials would be a lack of data[22] and lower number of participants[18,19,22,26] when compared to the other trials included. Random allocation for participants was used in all trials included and participants and examiners were blinded during the trials.

DISCUSSION

In summary, the results of these studies showed some evidence that supplementation with curcumin C3 complex with bioperine and nano curcumin lowers CRP. While the findings from these studies exhibit progressive first steps in understanding clinical applications of curcumin, limitations of studies limit conclusions. Study samples were small in 4 of the trials[18,19,22,26] and the duration of 4 of the trials[22,24-26] were 6 weeks or less. Differences in formulation and dosage also contribute to limitations and effect consistency across trials. Nano curcumin and Curcumin C3 complex with bioperine exhibit better bioavailability and nano curcumin appears to be more effective in lower doses (80-120mg) when compared to curcumin alone.[20,21,23,25]

C-reactive protein levels are an indication of the inflammatory state in the human body and can be related to acute inflammation, infection and autoimmunity.[11] CRP values will vary widely from person to person. 3-10 mg/L levels are considered to be in the category of low grade inflammation resulting in metabolic stress and are conducive with atherosclerosis, insulin resistance, hypertension, etc. Clinically significant levels or CRP equate to ≥ 10 mg/L and levels above 100 mg/L indicate severe infection.[17] In addition to serving as a marker for acute infection, elevated CRP levels have been associated with chronic conditions such as cardiovascular disease. It is believed that while acute inflammation can be advantageous in promoting healing and recovery, chronic inflammation can be detrimental and is thus connected with many chronic conditions. Chronically elevated CRP is indicative of chronic inflammation and its early detection may help in the prevention and treatment of such conditions. It is believed that CRP is stimulated by Interleukin-6 during times of trauma, or disease, therefore CRP can be reflective of overall systemic inflammation without having to report multiple biomarkers.[11,12,16]

Limitations

Limitations in the studies included in this review may be due to lack of proper control for confounding variables such as exercise, use of other supplements, use of over-the-counter medications, or other behaviors that may impact inflammation. Another limitation of homogeneity in participant populations. Out of the 9 trials, curcumin was tested in four Hemodialysis trials[18-21] two sulfur mustard intoxication trials[24,25] two cardiovascular trials[22,23] and one osteoarthritis trial.[26] Implications for the use of curcumin in healthy and subclinical populations are therefore challenging to determine.

Recommendations for Future Research

Future studies should utilize bioavailable curcumin formulas and should study healthy, subclinical populations and populations with chronic disease states in order to determine potential benefits of curcumin supplementation.[20,23-26] Dosage needs to be established for adequate treatment however tolerability of doses (84.4 mg- 2.5g) across trials was acceptable with minimal participant drop out and side effects. This will lead to better information for dosage and treatment for different disease states that are affected by inflammation.

CONCLUSION

Out of the 9 trials included in this systematic review, 5 of them utilized bioactive components, bioperine, nano, with the curcumin.[20,23-26] The results of this systematic review suggest that bioactive curcumin may be effective in lowering CRP in individuals suffering from inflammatory conditions Overall Bioactive Curcumin/ Curcumin with Bioperine may be viable alternative treatments for lowering the primary marker of systemic inflammation, CRP.

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