Research Article

Evaluation of the Effect of Curcumin Added to Standard Treatment on Outcomes in Patients with Mild to Moderate Covid-19 Infection

Manjusha Patankar[1†], Pradyut Waghray[2,3] and Kunal Waghray[3]

ABSTRACT

Background: SARS-CoV activates the immune cells to secrete inflammatory cytokines into pulmonary vascular endothelial cells. There is growing evidence on the inhibitory actions of curcumin on inflammatory cytokines.

Methods and findings: 131 patients were enrolled in the retrospective study. Of these, 77 patients were given the test drug Curcumin and Standard of Care (SOC) (Group 1) and 54 patients were given SOC (Group 2). Parameters of assessment included change in markers of inflammation DIMER, CRP, LDH, S. Ferritin and IL-6 as compared to baseline and symptom resolution.

Result: Group 1 had higher levels of DIMER, CRP, LDH, S. Ferritin and IL-6 at baseline. Yet, post treatment the curcumin treated patients had a significantly greater reduction in inflammatory markers as compared to group 2. IL-6 levels reduced significantly in both the groups (6.51 ± 3.93 at baseline to 3.04 ± 1.05 in Curcumin group *versus* 3.54 ± 1.71 at baseline to 2.23 ± 1.19; P<0.001 in the SOC group). Curcumin treated patients had higher levels of markers of disease severity and had higher comorbidities.

Conclusion: Bio-availability enhanced curcumin added to standard treatment significantly lowered the biological markers of inflammation in mild to moderate COVID-19 patients with comorbidities and also reduced time to symptom resolution.

Keywords: COVID-19; Curcumin; Bioavailability

Introduction

The outbreak of "CoronaVirus Disease 2019" (COVID-19), which originated in Asia, has become a pandemic. The COVID-19 pandemic, due to the novel severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), has resulted in an increase in hospitalizations for pneumonia with multi-organ disease all over the world [1]. SARS-CoV-2 can cause critical pneumonia in some patients, which is difficult to treat and may lead to multiple organ failure. Risk factors associated with mortality include old age, obesity, diabetes, and hypertension [2].

SARS-CoV activates the immune cells to secrete inflammatory cytokines into pulmonary vascular endothelial cells. Serious COVID-19 is associated with dysregulated inflammation [3]. COVID-19 patients have higher serum levels of cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-6 and IL-10) and CRP than control individuals [4]. Acute Respiratory Distress Syndrome (ARDS) is a clinical syndrome associated with pulmonary edema, severe arterial hypoxemia, and impaired carbon dioxide excretion, and finally leading to respiratory failure. It may occur due to a pulmonary or extra pulmonary infectious or noninfectious insult. Post-COVID, some patients with moderate to severe COVID suffer from pulmonary fibrosis and continue to have respiratory symptoms [5].

The Indian Council of Medical Research treatment protocols for COVID -19 are regularly updated and have ensured a uniform evidence based approach to the management of different severities of COVID-19. Yet challenges still remain and the search has been on for better treatments or adjunctive medications.

Curcumin, a natural polyphenolic compound, could be a potential treatment option for patients with coronavirus disease There is growing

[1]Clinical Medcine Infomatics, India

[2]Kunal Institute of Medical Specialities Pvt. Ltd. Hyderabad, India

[3]Senior consultant Apollo hospitals Hyderabad, India

Author for correspondence: Dr. Manjusha Patankar, Director, Clinical Medcine Infomatics, Maharashtra, India, Tell: +918693089090; E-mail: manjusha.patankar108@gmail.com

evidence on the inhibitory actions of curcumin on inflammatory cytokines [6]. Curcumin blocks the essential signals which regulate the expression of various pro-inflammatory cytokines such as nuclear factor-κB and MAPK pathways [7]. Curcumin has anti-inflammatory and anti-fibrotic effects by virtue of reducing the expression of chemokines and cytokines involved in lung infection such as IFNγ, MCP-1, IL-6 and IL-10 [8].

Methods

Study design

A retrospective, observational study was conducted in a tertiary care hospital.

Patient population

All patients admitted with COVID 19 disease during the period June 2020 to June 2021 were included in the study. Patients included in the study were diagnosed with COVID-19 infection of mild or moderate categories (WHO classification). All patients aged 18-90 years with the diagnosis of Covid-19 based on the PCR test were enrolled in the study. The exclusion criteria included patients <18 years of age, patients presenting more than 7 days after their onset of symptoms, pregnant or lactating women, patients with a history of hypersensitivity to turmeric or curcumin formulations or concomitant disease including severe renal failure (eGFR<30 ml/min), hepatic failure (Child-Pugh Score B or C), heart failure (EF<40%), chronic lung disease, active malignancy, immunosuppresed patients, and patients with active gastrointestinal bleeding. The study was conducted in accordance with the principles of good clinical practice.

Treatment

The patients were treated with standard treatment protocol as per the Indian Council of Medical Research (ICMR) guideline for the management of COVID-19 infections.

Treatment groups

The patients received either of two treatments added to the standard treatment protocol. One group received curcumin (Group 1) while the second group received only the standard treatment protocol (Group 2). Curcumin 500 mg tablet with enhanced bioavailability was provided by Edence Life Sciences.

Parameters of assessment

Primary assessment parameters were comparison of the change in biomarkers as compared to baseline. The secondary assessment parameters were comparison of the effect on symptom resolution.

Results

A total of 131 patients were enrolled in the study. Of these 77 patients were given the test drug

Table 1: Age distribution of patients enrolled in the study.

Age group (years)	Number	Percentage
18-30	41	31.30%
31-40	20	15.30%
41-50	22	16.80%
51-60	18	13.70%
61-70	20	15.30%
71-80	9	6.90%
81-90	1	0.80%

Table 2: Prevalence of symptoms.

Symptom	% patients with symptom
Mild fever	7.6
Fever	86.30%
High fever	6.10%
Cough	16.80%
Dry cough	12.20%
Chills	2.30%
Myalgia	19.80%
Nausea	1.50%
Sore throat	6.90%
Diarrhea	3.80%
Body ache	18.30%

Curcumin and Standard of Care (SOC) and 54 patients were given SOC. The mean age of the patient enrolled in the study was 43.46 years ± 16.81 years. The age distribution indicated that the most frequent age group was 18 years-30 years (**Table 1**).

A male preponderance was observed (60.3% *vs* 39.7%). 86% of patients included in the study had fever as the predominant symptom followed by loss of smell (24.4%) and los of taste (22.1%) (**Table 2**). Diabetes (17.6%) and hypertension (19.8%) were the most common comorbid diseases (**Figure 1 and Table 3**).

Group 1 had higher levels of D-DIMER, CRP, LDH , S. Ferritin and IL-6 at baseline. Yet , post treatment the curcumin treated patients had a significantly greater reduction in D- DIMER, CRP, LDH, S. Ferritin, IL-6 a compared to group 2 (**Table 4**). Non-Parametric tests were used to make statistical inference as data were not normally distributed. Wilcoxon-Mann-Whitney Test was used to compare the two groups in terms of IL-6 , LDH, CRP and D-Dimer at each of the timepoints. Friedman test was used to explore the change in IL-6 over time within each group.

Inspite of curcumin treated patients having high levels of markers of disease severity and comorbidities. there was no significant difference in symptom resolution between the two treatment groups or the time to swab negative result (**Table 5**).

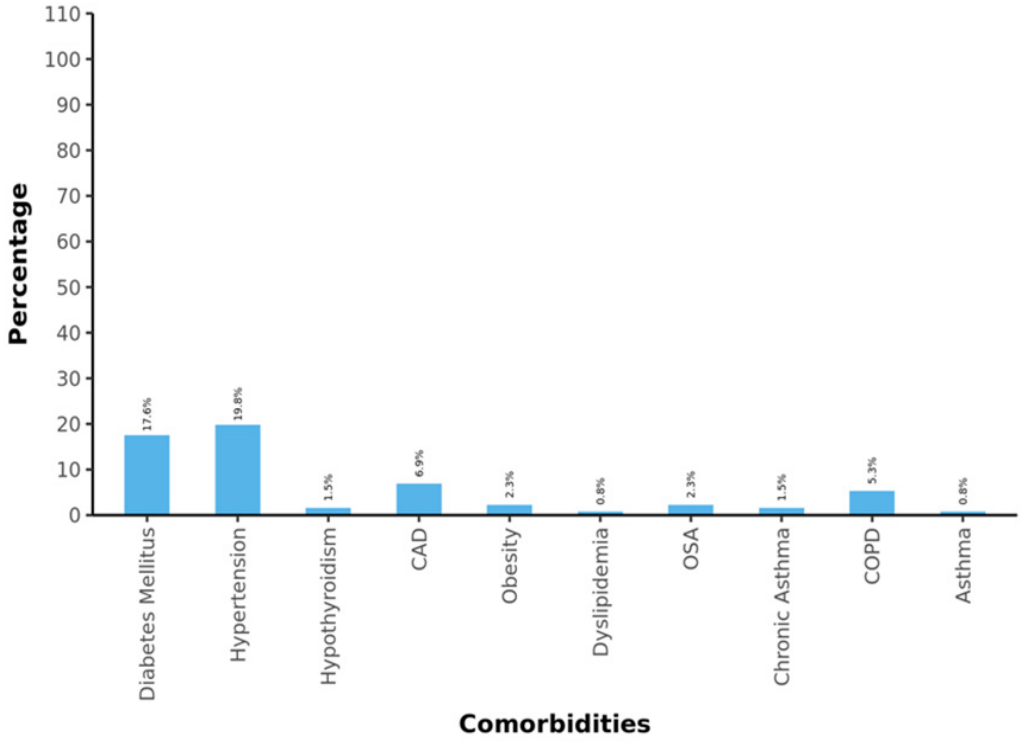

Figure 1: Comorbid diseases.

Table 3: Comorbidities in the two groups and effects of treatment.

	Std treatment + Curcumin (% patients) (Group 1)	Std Treatment (% patients) (Group 2)	p
		(% patients) (Group 2)	
Hypertension	0.325	0.019	<0.01
Diabetes	0.1679	0.0076	<0.01
Hypothyroidism	0.026	0	0.52
Coronary artery disease	0.117	0	0.01
Obesity	0.039	0	0.2
Dyslipidemia	0.013	0	0.1
Obstructive sleep apnea	0.039	0	0.2
Chronic asthma	0.026	0	0.5
Chronic obstructive pulmonary disease	0.091	0	0.04

Table 4: Comparison of biological markers pre and post treatment between the two groups.

	Baseline	Repeat 1	Repeat 2
D Dimer (ng/ml)			
Group1	521.48 ± 166.14	377.74 ± 102.59	NA
		P<0.001	
Group 2	348.96 ± 119.17	285.06 ± 96.80	NA
		P<0.001	
LDH (U/L)			
Group1	440.75± 194.54	237.01± 91.67	NA
		P<0.001	
Group 2	274.78 ± 94.45	184.00 ± 71.64	NA
		P<0.001	
CRP			
Group1	10.21 ± 6.45	5.38 ± 2.71	3.74 ± 1.47
		P<0.001	P<0.001
Group 2	5.05 ± 3.72	3.47 ± 2.00	2.42 ± 1.18
		P<0.001	P<0.001
S. Ferritin			
Group1	490.81 ± 173.47	265.66 ± 108.13	NA
		P<0.001	
Group 2	315.59 ± 114.01	190.93 ± 76.69	NA
		P<0.001	
IL-6			
Group 1	6.51 ± 3.93	4.18 ± 2.21	3.04 ± 1.05
		P<0.001	P<0.001
Group 2	3.54 ± 1.71	2.88 ± 1.46	2.23 ± 1.19
		P<0.001	P<0.001
NA: Not available			

Table 5: Time to symptom resolution and swab negative results.

	Std treatment + Curcumin (% patients) (Group 1)	Std Treatment (% patients) (Group 2) (% patients) (Group 2)	p
Time to symptom resolution (Days)	8.14 ± 2.63	7.33 ± 3.67	0.203
Time to negative swab (Days)	13.71 ± 2.91	12.22 ± 2.72	0.01

Discussion

The widespread COVID-19 pandemic has lead to repurposing of drugs.The key pathologic issues to be addressed in COVID disease are inflammation and raised cytokines.

Curcumin, is an active constituent of rhizomes of *Curcuma longa* (turmeric). It is a hydrophobic polyphenol [9-12]. Curcumin could be a potential treatment option for patients with coronavirus disease. Curcumin has several pharmacological effects such as antioxidant, anticancer, antibacterial, antiviral, and antidiabetic effects [13,14] as well as anti-inflammatory activity [15]. The transformation of curcumin into carbon quantum dots could boost antiviral effects of curcumin with different mechanisms [16]. Carbon quantum dots have efficacy against Human Coronavirus (HCoV) by inhibiting the entry receptor of HCoV-229E [17].

But one aspect of curcumin to consider is the fact that its bioavailability is low and this can adversely affect its clinical efficacy. The bioavailability of curcumin can be enhanced by several methods that increases the bioavailability by as much as 100 fold as compared to native curcumin. Improved bioavailability of formulated curcumin products is due to improved solubility,stability and possibly low first-pass metabolism [18]. Two meta-analyses of randomized controlled trials have shown that curcumin reduced circulating IL-6 and TNF-α levels which are the key inflammatory mediators and are found to be increased in inflammatory diseases. The inhibitory effects of curcumin on TLRs, NF-κB, cytokines, chemokines, bradykinin, oxyradicals, Transforming Growth Factor-beta1 (TGF-β1), Cyclooxygenase (COX), Plasminogen Activator Inhibitor-1 (PAI-1), IL-17A, and Caspase-3 (Cas-3) have been proven [19].

In severe COVID-19 infection, pneumonia may be associated hypoxemia, which, can disturb cell metabolism. This leads to acidosis and oxidative stress destruction of the phospholipid layer of the cell membrane [20]. Hence, a drug supplement that has antioxidant properties will be beneficial for these patients and curcumin has a potent antioxidant effect [21-23]. Curcumin increased the Superoxide Dismutase (SOD) level and reduced Malondialdehyde (MDA) level in acute lung injury in preclinical studies [24]. Similarly, another study conducted demonstrated that curcumin increased SOD activity and decreased MDA content in the lung in acute injury induced by sepsis [25]. Both antiapoptotic and antifibrotic effects of curcumin have been demonstrated in preclinical studies. Curcumin inhibits the activity of bradykinin by inhibiting the COX enzyme and thus reduces cough. Curcumin inhibits the cellular inflammatory response by reducing the cytokine/chemokine expression through the NF-κB pathway and fibrotic response during the regeneration phase of the disease through modulation of the TGF-ß pathway [6].

The current study demonstrated that curcumin significantly lowered the biological markers of inflammation COVID-19 such as LDH, CRP, D-DIMER. Administration of curcumin along with the standard treatment protocol improved outcomes of the patients. The clinical efficacy of the native curcumin is weak due to its low bioavailability and high metabolism in the gastrointestinal tract. Recently, different formulations with improved bioavailability of curcumin have been developed. Better bioavailability of these new formulated curcumin products is attributed to improved solubility, stability and possibly low first-pass metabolism [18].

Conclusion

Curcumin is a potent antioxidant and can reduce the lung inflammation in COVID-19 patients. Curcumin inhibits the release of inflammatory cytokines and reduces the biological markers of inflammation. Curcumin added to standard treatment can help relieve symptoms such as cough and improve outcomes of treatment in COVID-19 patients.

The weak bioavailability of curcumin can adversely affect its clinical efficacy. Bioavailability enhanced curcumin added to standard treatment significantly lowered the biological markers of inflammation in mild to moderate COVID-19 patients with comorbidities and also reduced time to symptom resolution. Curcumin can be a useful adjunctive therapy to add on to the treatment regimen in patients with mild to moderate COVID.

References

1. Zahedipour F, Hosseini SA, Sathyapalan T, et al. Potential effects of curcumin in the treatment of COVID-19 infection. Phytother Res 34, 2911-2920 (2020).
2. Babaei F, Nassiri-Asl M, Hosseinzadeh *H. Curcumin* (a constituent of turmeric): New treatment option against COVID-19. Food Sci Nutr 8, 5215-5227 (2020).
3. Soni VK, Mehta A, Ratre YK, et al. Curcumin, a traditional spice component, can hold the promise against COVID-19? Eur J Pharmacol 886:173551 (2020).
4. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 122, 2731-2740 (2012).
5. Ferreira VH, Nazli A, Dizzell SE, et al. The anti-inflammatory activity of curcumin protects the genital mucosal epithelial barrier from disruption and blocks replication of HIV-1 and HSV-2. PLoS One 10, e0124903 (2015).
6. Avasarala S, Zhang F, Liu G, et al. Curcumin modulates the inflammatory response and inhibits subsequent fibrosis in a mouse model of viral-induced acute respiratory distress syndrome. PLoS One 8, e57285 (2013).
7. Akbar MU, Rehman K, Zia KM, et al. Critical review on curcumin as a therapeutic agent: From traditional herbal medicine to an ideal therapeutic agent. Critical Reviews in Eukaryotic Gene Expression 28, 17-24 (2018).
8. Alamdari N, O Neal P, Hasselgren PO. Curcumin and muscle wasting: A new role for an old drug? Nutrition 25, 125-129 (2009).
9. Sahebkar A, Cicero AFG, Simental Mendía LE, et al. Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis of randomized controlled trials. Pharmacological Res 107, 234-242 (2016).
10. Hosseini A, Hosseinzadeh H. Antidotal or protective effects of Curcuma longa (turmeric) and its active ingredient, curcumin, against natural and chemical toxicities: A review. Biomed Pharmacotherapy 99, 411-421 (2018).
11. Fan Z, Yao J, Li Y, et al. Anti-inflammatory and antioxidant effects of curcumin on acute lung injury in a rodent model of intestinal ischemia reperfusion by inhibiting the pathway of NF- κB. Int J Clin Exp Pathol 8, 345s1-3459 (2015).
12. Moghadamtousi SZ, Kadir HA, Hassandarvish P, et al. A review on antibacterial, antiviral, and antifungal activity of curcumin. BioMed Res Int 186864 (2014).
13. Cheng K, Yang A, Hu X, et al. Curcumin attenuates pulmonary inflammation in lipopolysaccharide induced acute lung injury in neonatal rat model by activating peroxisome proliferator-activated receptor γ (PPARγ) Pathway. Med Sci Monitor 24, 1178-1184 (2018).
14. Lin CJ, Chang L, Chu HW, et al. High amplification of the antiviral activity of curcumin through transformation into carbon quantum dots. Small (Weinheim an Der Bergstrasse, Germany) 15, e1902641 (2019).
15. Loczechin A, Séron K, Barras A, et al. Functional carbon quantum dots as medical countermeasures to human coronavirus. ACS Applied Materials & Interfaces, 11(46), 42964-42974 (2019).
16. Derosa G, Maffioli P, Simental Mendía, et al. Effect of curcumin on circulating interleukin-6 concentrations: A systematic review and meta-analysis of randomized controlled trials. Pharmacological Res 111, 394-404 (2016).
17. Soleimani V, Sahebkar A, Hosseinzadeh H. Turmeric (*Curcuma longa*) and its major constituent (curcumin) as nontoxic and safe substances: Review. Phytotherapy Res 32, 985-995 (2018).
18. Sahebkar A, Cicero AFG, Simental Mendía LE, et al. Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis of randomized controlled trials. Pharmacological Res 107, 234-242 (2016).
19. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virology 92, 552-555 (2020).
20. Abrahams S, Haylett WL, Johnson G, et al. Antioxidant effects of curcumin in models of neurodegeneration, aging, oxidative and nitrosative stress: A review. Neurosci 406, 1-21 (2019).
21. Farzaei M, Zobeiri M, Parvizi F, et al. Curcumin in liver diseases: A systematic review of the cellular mechanisms of oxidative stress and clinical perspective. Nutrients 10, 855 (2018).
22. Mary CPV, Vijayakumar S, Shankar R. Metal chelating ability and antioxidant properties of curcumin-metal complexes-A DFT approach. J Molecul Graphics Modelling 79, 1-14 (2018).
23. Fan Z, Yao J, Li Y, et al. Anti-inflammatory and antioxidant effects of curcumin on acute lung injury in a rodent model of intestinal ischemia reperfusion by inhibiting the pathway of NF- κB. Int J Clin Experimental Pathol 83451-3459 (2015).
24. Xiao X, Yang M, Sun D, et al. Curcumin protects against sepsis-induced acute lung injury in rats. J Surgical Res 176 e31-39 (2012).
25. R. Jamwal. Bioavailable curcumin formulations: A review of pharmacokinetic studies in healthy volunteers. J Integrative Med 16, 367-374 (2018).