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The Effect of Curcumin Adjuvant Therapy on Pulmonary Function and Levels of Interleukin-6 (IL-6) and Superoxide Dismutase-3 (EC-SOD3) in Patients with Chronic Bronchial Asthma

Sura Abbas Khdair[1*], Manal Khalid Abdulridha[1], Mostafa Abdalfatah Shafek[2]

1. Department of Clinical Pharmacy, College of Pharmacy, Al-Mustansiriyah University, Baghdad, Iraq, Palestine Street P.O. Box: 14022
2. Department of Internal Medicine, Al-Yarmouk Teaching Hospital, Jinub Street, Baghdad, Al-Karkh, Al-Yarmouk, Iraq

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*Corresponding author
Sura Abbas Khdair

Email:
pharm.sura.abbas@uomustansiriyah.edu.iq

ABSTRACT

This study was designed to evaluate the effectiveness of curcumin supplements as antioxidant and anti-inflammatory in patients with chronic bronchial asthma. Forty patients diagnosed with chronic bronchial asthma were enrolled in this study. 17 patients were allocated in group 1 with conventional therapy of asthma and 23 patients were put in group 2 with conventional therapy of asthma combined with 750mg curcumin supplement twice daily for two months. Pulmonary function test, asthma control test, and measurements of serum interleukin-6 and serum extracellular superoxide dismutase 3 were performed before and after two months in both study groups. After two months, the mean values of pulmonary function test (spirometry) and asthma control score showed a significant increase compared to pre-treatment values in group 2 patients ($P<0.01$). After two months, there was a marked decrease in the level of interleukin-6 in group 2 patients ($p< 0.05$) compared to the group 1 patients. The mean level of superoxide dismutase 3 did not show any increase in both study groups. Curcumin supplement produced improvement in pulmonary function of patients with chronic bronchial asthma along with the reduction in inflammatory status. No change in endogenous oxidative status after curcumin supplementation.

Keywords: chronic bronchial asthma, pulmonary function, curcumin supplement, interleukin-6, superoxide dismutase 3.

INTRODUCTION

Supplements were used in addition to conventional therapy in patients with chronic asthma (Abbas, *et al*., 2017). Natural products were tested by many studies to be used as a supplemental medical treatment in humans such as curcumin. These products are relatively non-toxic and have therapeutic doses well below their toxic levels (Fadus, *et al*., 2017). Current evidence suggests that curcumin is a highly pleiotropic molecule with numerous targets and mechanism of action. It has properties that alter the activity of enzymes, growth factor receptors, cofactors, and other molecules (Fadus, *et al*., 2017). Curcumin may participate in the management of different pulmonary diseases. its anti-inflammatory, anti-oxidant, anti-fibrotic and anti-cancer effects mediated by modification of some mediators (such as NF- kB and AP-1) (Lelli, 2017).

Many studies have explored the important role of curcumin in respiratory diseases caused by inflammation (Kurup and Barrios, 2008) such as acute lung injury *(*Tyagi, *et al,* 2014; Xu*, et al*., 2015), asthma (Khdair, *et al*., 2019; Lelli, 2017), chronic obstructive pulmonary disease (COPD) (Panahi *et al*, 2016), and pulmonary fibrosis (Smith *et al*., 2010). According to the previous data from various studies, human trials about the efficacy of oral curcumin in asthma are very few. Hence, the present study was undertaken to clinically evaluate whether or not oral curcumin supplement can improve pulmonary function and disease control in asthmatic patients concomitantly with its anti-inflammatory and antioxidant effect in those patients.

METHOD AND MATERIALS

Patients

This is a prospective randomized-controlled open-label interventional study. A total of forty candidate patients with chronic bronchial asthma were enrolled in the study after a full explanation of the purpose of the study and the possible results of the study during their visit to the hospital. Those patients were supervised by a pulmonary specialist and treated according to their disease severity and clinical practice guidelines. Approval of institutional ethical committee (86390 at 22\10\2017) was obtained according to Helsinki declaration 2000 and written informed consents were taken from all patients. Those patients were randomly allocated into two groups; group 1 included 17 asthmatic patients received regular asthma drugs through different disease stage and severity for two months, and group 2 included 23 asthmatic patients received regular asthma drugs through different disease stage and severity for two months beside 750mg curcumin capsule (combined with 5mg piperine) twice daily for two months. Curcumin, when taken orally as it is without any modification, will be absorbed very poorly and the serum level of curcumin not significantly increased even at doses up to 8000 mg (Sharma *et al*., 2006, Lao *et al*., 2006). Therefore, to resolve this problem, modifications in curcumin supplements are required. One of these modifications is a combination with piperine which is an alkaloid found in black pepper (Piper nigrum) and long pepper (Piper longa) (Fadus *et al*., 2016). The presence of piperine contributes to a 154% increase in the systemic bioavailability of curcumin in rats while in human 20 mg piperine produced a 2000% increase in the systemic bioavailability of curcumin (Aggarwal *et al*., 2007) due to inhibition of hepatic and intestinal glucuronidation of curcumin by piperine (Fadus *et al*., 2016). Curcumin doses used in the previous studies ranged from 500-1000 mg twice daily (Abidi *et al*., 2014, Jusufovic *et al*., 2017, Kim *et al*., 2011).

Conventional therapy used in this study included many drugs. According to the severity of the disease, patients were stage 2 or 3 of asthma. Patients on bronchodilator reliever medication such as β2-agonist (Salbutamol), also, inhaled preventer medication such as corticosteroid/long-acting β2-agonist combination, leukotriene antagonist (montelukast), and systemic corticosteroid (Prednisolone) for a short duration on acute exacerbation.

Methods

Pulmonary function test (PFT) using spirometry was done including forced expiratory volume in one second (FEV1) (predicted and measured), forced vital capacity (FVC), and (FEV1/FVC) ratio were measured. Asthma control was assessed by using asthma control test (ACT) in which the patients were required to answer five questions regarding the use of inhaled rescue medication, frequency of shortness of breath, the occurrence of asthma symptoms in the night or early morning, the effect of asthma on daily activities and self-assessment of asthma control in the past 4 weeks. Each question was pointed from 1 to 5 points. An (ACT) score of (25) points was considered well controlled, an (ACT) score between (20-24) points was considered on target, and when the score (≤20) points, asthma was considered off-target and required treatment adjustment (*Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. (US)*, 2007). Measurements of serum IL-6 and serum EC-S0D3 were done using a commercial enzyme-linked immunosorbent assay (ELISA) kit.

All those parameters were investigated at baseline and after two months of treatment.

Statistical analysis

The data were analyzed using the following software: Microsoft Excel, Minitab v17, and IBM SPSS v24. Results reported in this study were expressed as mean ±SD. Chi-square test was used to clarify the significance of differences between demographic variables while another test called paired t-test was used to analyze values of pre- and post-treatment results; lastly, comparison between pre- or post-treatment between Groups 1 and 2 was done by two-sample t-test. The probability values of less than 0.05 were considered significantly different.

RESULTS AND DISCUSSIONS

Forty patients enrolled in this study included 14 males (35%) and 26 females (65%). The mean age for group 1 patients was 44.94±12.24 years old while for group 2 patients was 44.83±12.57 years old and the age range in group 1 was 20-64 years while in group 2 was 23-67 years. There was no statistically significant difference between study groups regarding gender, age, family history, comorbid diseases, and asthma symptoms onset ($p>0.05$) (Table I).

Table I. Demographic data and disease characteristics

Variable	Study groups		p-value
	Group 1 (n=17)	Group 2 (n=23)	
Gender	n(%)	n(%)	
Female	10 (58.8)	16 (69.60)	0.481^{NS}
Male	7 (41.2)	7 (30.40)	
Total	17(100)	23(100)	
Age (years old)	44.94±12.24	44.83±12.57	0.991^{NS}
Age range (years)	(20-64)	(23-67)	1.00 ^{NS}
Family history			
Positive	9 (52.9)	9 (39.1)	0.385 ^{NS}
Negative	8 (47.1)	14 (60.9)	
Comorbid disease			
Positive	8 (47.1)	6 (26.1)	0.169 ^{NS}
Negative	9 (52.9)	17 (73.9)	
Asthma symptoms onset			
Childhood-onset	10 (58.8)	16 (69.6)	0.481 ^{NS}
Adult-onset	7 (41.2)	7 (30.4)	

Data in this table presented in which mean ±SD, (n) is number of patients and (%) is percentage. Chi-square test numericalvalues to compare between group1 and group 2, where, NS: not significant (p>0.05), significant difference (p<0.05), **Highly significant difference (p<0.01.)

The mean values of both measured and percentage of the predicted value of FEV1 revealed no significant difference at the beginning of study and after two months of treatment (p<0.05) between study groups. There is a significant increase in the post-treatment value of FEV1 in comparison to the pre-treatment value in group 1 patients (p<0.05). Nevertheless, the increase in FEV1 in group 2 patients was highly significant (p<0.01) after two months. The post-treatment value of the percentage of predicted FVC was increased significantly in both groups in comparison to the pre-treatment value (p<0.05).

The mean value of FVC (presented as measured and percentage of predicted value) showed no significant difference between both groups at baseline and after two months treatment period (p>0.05). The measured value of FVC in group 2 patients increased significantly post-treatment compared to the pre-treatment value (p<0.05). Group 2 patients have shown a highly significant increase in (FEV1/FVC) ratio after two months of treatment as compared to pre-treatment values (p<0.01). However, there was no significant difference in the mean value of (FEV1/FVC) ratio at baseline and after two months from starting the intervention between study groups (p>0.05). Mean of both measured and percentage of predicted value of PEF (post treatment in group1) post treatment in group 1 showed a significant increase compared to the pre-treatment value (p<0.05) while group 2 patients showed a highly significant increase in PEF post treatment as compared to pretreatment value (p<0.01). However, PEF mean values showed no significant difference at baseline and after two months of treatment between group 1 and group 2 (p>0.05) (Table II).

There was no significant difference in the mean value of ACT at the baseline between study groups (p> 0.05) but a significant difference was found between group 1 and group 2 after two months (p<0.05). Group 2 showed a highly significant increase in the post-treatment mean value of ACT compared to the pre-treatment value (p<0.01) (Table III).

The mean level of serum IL-6 showed no significant difference at the baseline between study groups (p>0.05) while there was a significant difference between group 1 and group 2 after completion of the two months study (p<0.05). There was no significant difference in the mean level of serum SOD 3 before and after two months between study groups (p>0.05); (Table IV).

Table II. Effect of conventional therapy alone and in combination with curcumin supplement on PFT after two months.

FEV1 (L)(meas.)	**Group1 (n=17)**	**Group2 (n=23)**	**p-value**
Pre-treatment	1.66±0.56	1.45±0.59	0.272NS
Post treatment	2.03±0.91	1.90±0.67	0.595NS
FEV1(L)(% pred.)			
Pre-treatment	55.35±18.80	50.00±15.72	0.334NS
Post treatment	66.00±21.75	65.22±16.65	0.898NS
p-value	0.011*	0.001**	---------
FVC(L)(meas.)			
Pre-treatment	2.30±0.61	2.19±0.80	0.648NS
Post treatment	2.63±0.92	2.53±0.87	0.747NS
p-value	0.052	0.044*	-------
Percent of change	+12.5 %	+13.4 %	-------
FVC (L)(% pred.)			
Pre-treatment	64.12±17.75	63.57±17.71	0.923NS
Post treatment	71.76±17.57	73.04±15.75	0.810NS
FEV1/FVC (%)			
Pre-treatment	70.9±10.0	65.90±8.42	0.095NS
Post treatment	75.3±13.2	75.5±12.3	0.952NS
PEF(L/S) (meas.)			
Pre-treatment	3.31±1.15	2.92±0.85	0.226NS
Post treatment	4.18±2.09	4.06±1.35	0.824NS
p-value	0.047*	0.001**	---------
Percent of change	+20.8 %	+27 %	---------
PEF (L/S)(%pred.)			
Pre-treatment	45.76±19.06	42.43±10.57	0.485NS
Post treatment	56.00±23.18	57.91±16.17	0.760NS
p-value	0.041*	0.001**	-------
Percent of change	+18.2	+26.7 %	-------

Data in this table illustrated as mean ± SD, meas: measured value, pred: % of predicted value. A two-sample t-test utilized to analyze results between group 1 and group2 patients while paired t- test used to compare between values pre and post treatment within the same group. NS: no significant differences (p> o.o5),(*) indicate significant difference in which p value less than 0.05,.lastly, (**) indicate presence of highly significant differences in which p value less than 0.01. The normal values of PFTs in normal healthy adult are as follow: FEV1 3.2 L to 4 L, FVC 4 to 5 L, FEV1/FVC% is 75%-85% and PEF 550 TO 770 L/min (Self TH et al., 2013).

Table III. comparison between the effect of standard asthma treatment alone and in combination with supplement of curcumin on ACT in the end of study

ACT	**Group1 (n=17)**	**Group2 (n=23)**	**p-value**
Pre-treatment	13.35±4.14	11.78± 3.22	0.185 NS
Post treatment	16.12± 4.78	20.00±4.32	0.011 *
P-value	0.105 NS	0.001*	------
% of change	+17.1%	+41%	------

Data in this table illustrated as mean ± SD, meas: measured value, pred: % of predicted value. A two-sample t-test utilized to analyze results between group 1 and group2 patients while paired t- test used to compare between values pre and post treatment within the same group. NS: no significant differences (p> o.o5), (*) indicate significant difference in which p value less than 0.05,.lastly, (**) indicate presence of highly significant differences in which p value less than 0.01. •Score of 25(well done), Score between 20-24 (on target), Score less than 20 (off target).

Table IV. Effect of conventional therapy alone and in combination with curcumin supplement on IL-6 and EC-SOD3 levels after 2 months

Serum IL6 (pg/ml)	**Group1 (n=17)**	**Group2 (n=23)**	**p-value**
Pre-treatment	175±165	210± 201	0.564
Post treatment	315± 261	174±148	0.038*
P-value	0.077	0.463	------
Percent of change	+78%	-20.6%	------
Serum- SOD3 (ng/ml)			
Pre-treatment	74.5 ± 38.7	84.7 ± 41.5	0.43
Post treatment	58.77±34.85	63.6 ± 38.9	0.77
p-value	0.163	0.068	------
Percent of change	-21.1%	-33.1%	------

Through data analysis of the present study, the findings showed that the majority (65%) of the study participants were females and these results agreed with the finding of other studies (Ahmed, 2016; Baldaçara and Silva, 2017; Zein and Erzurum, 2015). Hormonal and immunological factors and/or differences in responses to environmental or occupational exposure according to the gender are all involved in the variations of results between male and female in this study (Zein and Erzurum, 2015). Also, all asthmatic patients were aged between 20-67 years old and were matched in the study groups.

More than 50% of patients in both study groups had a negative family history and this comes in contrast with many studies that provide evidence that the incidence of asthma during the first 27 years of life is strongly related to family history of asthma and the risk of personal asthma increased in relation to both parents' and siblings' asthma (Lajunen, *et al*., 2013) but the sample size in this study is small to compare. However, positive family history is a non-modifiable risk factor for asthma and other atopic diseases (Abbas, *et al*., 2018).

With reference to the results in the present study, the highest percentage of asthmatic patients (65%) were diagnosed as asthmatic in the childhood period. This finding was close to that done by Mirabelli *et al*. (2013) where 42% of adults with asthma reported the onset of asthma as occurring before the age of 16 (Mirabelli *et al*., 2013). This finding reflects the highest percentage of asthma among children as appeared in a study done by Al samarai *et al*. who demonstrated that 16 % of children from 25 different Iraqi primary schools aged between 11-14 years were diagnosed with asthma (Alsamarai *et al*., 2009). Reversible airway obstruction is considered when (FEV1/FVC) is less than 70% (0.70), and a healthy young adult typically has a PEF (peak expiratory flow) of 550 to 700 L/minute (9.2- 11.2 L/S) (Self, 2013.). In the present study, curcumin supplementation produced a significant increase in the measured and predicted values of FEV1, FVC, and PEF with a percent of change of (+23.3%, +12.9%, and +26.7%) for the predicted values respectively ($p<0.01$) compared with values in patients receiving standard bronchial asthma therapy. The ratio of FEV1/FVC was also increased by 12.7% in patients on curcumin supplementation. A comparable result was noticed in a study by Abidi *et al*. (2014), where the effect of addition of curcumin dose at 500 mg twice daily for 1 month in 30 patients receiving standard bronchial asthma therapy resulted in a highly significant increase in FEV1 ($p<0.05$). Abidi also assessed the severity of asthma symptoms as absent, mild, moderate, and severe with scores of 0, 1, 2, and 3, repectively, though were not much reliable and revealed no significant improvement in clinical symptoms (Abidi *et al*., 2014). Meanwhile, the value of ACT in the present study was highly improved after the curcumin supplement regimen only (increased by 41% vs 17.1%, $p<0.001$). In another study done by Jusufovic *et al*. (2017), curcumin at the dose of 500 mg twice daily in combination with medium-dose inhaled corticosteroid was assessed in 50 non-smoker patients with moderate partially controlled asthma for two months and compared to a parallel number of patients receiving only medium-dose inhaled corticosteroid. There was a highly significant

increase in the percentage of predicted FEV1 in the curcumin group (increased by 7% vs 2%) and ACT scores (19 % vs 13%) (p<0.0001) (Jusufovic, *et al*., 2017).

Those two studies considered FEV1 as the best indication of lung function (Jusufovic, *et al*., 2017; Self, 2013.). In contrast, an early study by Kim *et al*. (2011) found that supplementation of nine asthmatic patients with 1000mg of curcumin twice daily for 6 months did not result in significant improvement in the mean FEV1 value (p=0.0562)(Kim, *et al*., 2011). In a population-based study in China (2012) the effect of turmeric (curcumin)-rich curry dietary intake on pulmonary function was studied and of 2478 (smoker and non-smoker) subjects aged >55 years old, there were 76 patients with asthma and COPD who consumed curry very often (at least once a week or daily). It was found in this study that those patients had higher mean values of FEV1, FVC, and FEV1/FVC than other participants in the study, suggesting that the anti-oxidant and anti-inflammatory actions of curcumin might be particularly effective in protecting against pulmonary damage caused by smoking (Ng, *et al*., 2012).

Different inflammatory diseases associated with elevated level of IL-6 (Kishimoto, 2010). Based on the previuos facts, IL-6 considered as a general marker of inflammation together with TNFα and IL-1β, two other classical inflammatory cytokines (Rincon and Irvin, 2012). Increased levels of IL-6 in serum have been found in asthmatic patients and it is associated with lower lung function and more frequent asthma exacerbations (Peters *et al*., 2016; Rincon and Irvin, 2012). In the current study, the serum level of IL-6 decreased markedly in asthmatic patients receiving curcumin supplement (decreased by 20%) compared to the 78% increase in asthmatic patients receiving conventional treatment (p<0.05). 5mg only of piperine was found in the combination with curcumin to enhance its bioavailability while the anti-inflammatory effect of piperine required higher doses ranging from 20-100mg/kg (Bang, *et al*., 2009). Up to the best search, no data was available to compare the effect of curcumin on serum level of IL6 within asthmatic patients, except that studies that explored the anti-inflammatory effect of curcumin supplement in asthma measured other parameters such as C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) (Abidi, *et al*., 2014; Jusufovic, *et al*., 2017). On experiment level, curcumin was found to diminish airways remodeling in asthma when administered intraperitoneally (Karaman, *et al*., 2012). In a dose-dependent manner, curcumin cause reduction of epithelium and subepithelial smooth muscle thickness in mice at low dose and at the highest dose the effect on histopathological characteristics was comparable to that of dexamethasone (Karaman, *et al*., 2012). These histological effects of curcumin were confirmed by Zeng *et al*.(2013), who also reported that intraperitoneal administration of curcumin reduced the number of inflammatory cell infiltrated within the lungs and the proliferation of airway smooth muscle cell is inhibited in a dose-dependent manner by downregulating the extracellular signal-regulated kinase pathway (ERK) (Zeng, *et al*., 2013).

Superoxide dismutase is an enzyme with an essential function in protecting aerobic cells against oxidative stress (Comhair and Erzurum, 2010). In asthmatic lungs, the activity of SOD is lower compared with healthy controls and decreases further during an asthmatic attack (Comhair *et al*., 2005). Promising effect of curcumin on the measures of systemic oxidative stress such as decreased level of Malondialdehyde (MDA) and increased level of glutathione (GSH) was noticed in many diseases other than asthma in human (Panahi *et al*., 2016, 2017; Tabrizi *et al*., 2019). In the current study, oral curcumin supplement did not result in an increased serum EC-SOD3 level. In fact, EC-SOD3 level decreased in both groups. This finding may be due to a number of reasons. First, although EC-SOD is found in extracellular matrix space, it is bound to heparin sulfate proteoglycans of endothelial cell surfaces, and <1% of EC SOD is found in the serum (Comhair & Erzurum, 2010). Thus, EC-SOD contributes very little to serum SOD and the other isoforms of SOD (CuZnSOD and MnSOD) may reflect a better image on curcumin effect as they are released to the circulation during the normal turnover of cells and account for serum SOD activity (Comhair & Erzurum, 2010). Second, the best way to measure SOD activity in the lung epithelium is by bronchoscope, and by this method, it was found that SOD activity in the airway demonstrated a significant inverse correlation with airway reactivity as determined by percent change in FEV1 after a bronchodilator (Comhair *et al*., 2005), which is an invasive method. An experimental rat model with asthma receiving a high concentration of *Curcuma longa* extract

and dexamethasone produced a significant reduction in MDA and significant elevation in SOD serum activity compared to the control group (Shakeri *et al*., 2018).

A few limitations faced the present study including size of sample with different disease severity (stage1 and 2) which requires further study to proof the findings, patients duration of follow-up was short, as a longer period may be required to explore a good result, and it was difficult to perform bronchoscopy to obtain a better image on SOD activity more than serum sample. Considering that the interaction between pro-inflammatory and anti-inflammatory cytokines is complex, measurement of the full cytokine profile can reflect the cytokine-modulating effects of curcumin more accurately. The final limitation is the dietary intake was not monitored during the study with the possibility that some nutrients have inflammatory and anti-inflammatory properties.

CONCLUSION

According to this study, it is concluded that curcumin can improve lung function and asthma control together with a reduction of the inflammatory status without affecting oxidative status in patients with chronic bronchial asthma.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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