

# Curcumin improves step 4 asthma treatment: placebo-controlled, single blind study

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## Abstract

**Background:** Despite multistep efforts, many asthma patients remain symptomatic. Anti-inflammatory activities of curcumin are shown. Aim of the study was to analyse the impact of curcumin add-on therapy on inflammatory parameters, lung function, disease control and quality of life in asthma patients.

**Subjects and methods:** Three-months lasting study was done on 150 non-smokers with asthma, that were treated with stable, moderate dose of inhaled glucocorticoids (IGK) and divided into three groups (n=50 each): curcumin group (receiving curcumin 500 mg per os twice daily), placebo group (receiving placebo tablets) and control (non-intervention) group. Sputum eosinophils (sEo), blood eosinophils (bEo), high sensitive C-reactive protein (hsCRP), predicted forced expiratory volume in first second (FEV1%), Asthma Control Test (ACT) and mini Asthma Quality of Life Questionnaire (mAQLQ) were compared before and after study, as well as between groups.

**Results:** Before study, all followed parameters were similar between groups. After study, FEV1%, ACT and AQLQ were improved in all groups, but these improvements were more prominent in curcumin group than in placebo and control. Additionally curcumin group only showed improvement in sEo, bEo and hsCRP. Furthermore, curcumin group showed more frequent clinically significant improvement in ACT score (change>3) and in mAQLQ score (change≥0.5) when compared to placebo and control. On the other side, after study FEV1%, ACT, mAQLQ, hsCRP, sEo and bEo were similarly distributed among placebo and control group.

**Conclusion:** This is the first placebo controlled and single-blind study to suggest that add-on therapy with curcumin could improve lung function, disease control and quality of life in moderate partially controlled asthma. Future studies may benefit from a larger sample size, longer study duration, double blind design, different dose of curcumin and/or improvements in oral bioavailability.

**Keywords:** asthma, therapy, curcumin, placebo

## Introduction

Despite treatment with high dose of inhaled corticosteroids (ICS), inhaled long acting bronchodilators (LABA), and, even in some cases, systemic corticosteroids, a significant proportion of asthma patients remain symptomatic.<sup>1</sup> In a study performed in 2 European countries, asthma control was suboptimal in 56.5% of patients and associated with poorer asthma-related quality of life, higher risk of exacerbations and greater consumption of healthcare resources.<sup>2</sup> In Canada only 28.1% of patients showed well controlled asthma, while the majority of patients had partially controlled or even uncontrolled disease.<sup>3</sup> Asthma severity has often been based on prescribed treatment step. Patients prescribed Step 3-4 treatments are often described as having moderate asthma and those prescribed Step 4-5 as having moderate to severe asthma. However, this is only a surrogate measure, and it

causes confusion. From this reason, for epidemiological studies or clinical trials, it is preferable to categorize patients by the treatment step that they are prescribed, without inferring severity.<sup>4</sup> WHO has recognized herbal medicines as an essential building block for primary health care particularly in developing countries. In the past it has been reported that up to 40% asthma patients use herbal medicines.<sup>5</sup> It has been shown that curcumin exhibited anti-inflammatory activities<sup>6</sup> by down-regulating intercellular signalling proteins, such as protein kinase C,<sup>7</sup> modulating the activity of transcription factors like activating protein-1 (AP-1), suppressing NF-KB pathway, cyclooxygenases, lipoxygenase pathways and iNOS expression. It also inhibits transcription factor products such as signal transducer and activator of transcription (STAT), PPAR-g and down-regulates Janus kinases.<sup>8</sup> These pathways have been recognized to be involved

in the complex inflammatory asthma response.<sup>9</sup> Curcumin inhibits the activity of inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukins (IL-1, 2, 6, 8, 12), migration inhibitory protein,<sup>10</sup> eotaxin, monocyte chemoattractant protein (MCP)<sup>11</sup> and monocyte chemoattractant protein 3 from IL-1 stimulated human airway smooth muscle cells.<sup>12</sup> Curcumin is able to induce the expression and production of IL-10 and through this effect modulates the disease pathophysiology of conditions such as pain and neurodegenerative diseases, bowel inflammation, allergy, infections and cancer.<sup>13</sup> When added to *Der f* stimulated lymphocyte cell cultures from allergic asthmatic patients, curcumin inhibits *Der f*-induced lymphocyte proliferation and production of IL-2, IL-4, IL-5, and granulocyte macrophage colony stimulating factor.<sup>14</sup> In a mouse model of chronic asthma and oropharyngeal candidiasis curcumin was as effective as the prescription steroid dexamethasone and had equal ability to reverse ovalbumin induced histopathological airway changes due to inflammation.<sup>15</sup> Curcumin also decreased airway constriction and hyperreactivity in guinea pigs (20 mg/kg) when coadministered with ovalbumin.<sup>16</sup> It was confirmed that curcumin is a dual inhibitor of arachidonic acid metabolism, inhibiting both the enzymes 5-lipoxygenase and cyclooxygenase,<sup>17</sup> as well as inhibiting prostaglandin E<sub>2</sub>, leukotriene B<sub>4</sub> and leukotriene C<sub>4</sub>.<sup>18</sup> This makes curcumin acting in asthma similar to those in montelukast.<sup>19</sup> Some studies showed the clinical efficacy and safety of curcumin as an add on therapy in patients of mild to moderate asthma improving FEV<sub>1</sub> values and blood eosinophils,<sup>10</sup> but not ACT scores, use of rescue bronchodilator, dose of inhaled corticosteroid, exhaled NO and serum IgE and blood eosinophils.<sup>10,20</sup> The aim of this study was to analyse the impact of curcumin add-on therapy in patients requiring Step 4 Treatment on sputum and blood eosinophils count, lung function, disease control and quality of life in asthma patients.

## Subjects and methods

**Study design:** A prospective, randomised, single-blinded, placebo controlled and 3 months lasting study was conducted from December 2016 to May 2017 year in Polyclinic for Pulmonary Diseases of Public Medical and Educational Institution Tuzla, Bosnia and Herzegovina, whose Ethics Committee approved it (16-1-13421/19). All patients had given the written, signed informed consent prior of the study.

**Subjects:** 150 non-smokers with asthma were included. Before the enrolment into the study all subjects had been treated by GINA 3 Step treatment with low dose of ICS/LABA (250 mcg fluticasone propionate + 100 mcg salmeterol HFA, per day, divided in two doses) with inhaled salbutamol as needed during 3 months. At the very beginning of the study the ICS/LABA dose was increased up to GINA 4 Step treatment (moderate dose: 500 mcg fluticasone propionate + 100 mcg salmeterol HFA, per day, divided in two doses) with inhaled salbutamol as needed, based on asthma symptoms control. Before the increment of ICS/LABA dose, adherence and compliance to inhaled therapy were checked in all patients, by anamnesis of extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment, as well as by checking the technique of taking inhaled therapy. During next three months (observational period of this study) ICS/LABA dose was kept stable. Subjects were divided into three groups (n=50 each): 1. curcumin group receiving addition therapy with curcumin 500 mg *per os* twice daily, 2. placebo group (receiving placebo *per os* twice daily) and 3. control (non-intervention) group, receiving ICS/LABA with salbutamol only. Subjects in curcumin and placebo group were blinded to therapy added to basic GINA 4 therapy.

Additional therapy was: dietary curcumin tablets of 500 mg (curcumin group) and inert, sugar tablets (placebo group). Curcumin tablets were provided by ZADA pharmaceuticals in Bosnia and Herzegovina. The real content of curcumin and placebo tablets was known only to a physician, but not to a patient (single blind study).

**Inclusion criteria** were: 1. moderate to severe asthma, partially controlled on Step 3 defined by last GINA recommendations; 2. good adherence and compliance to inhaled therapy; 3. age of 18 years or more. **Exclusion criteria** were: 1. history of drug allergy; 2. pregnant women or nursing mothers; 3. significant concomitant diseases; 4. current smoking; 5. chest infection. Sputum eosinophils (sEo), blood eosinophils (bEo), high sensitive C-reactive protein (hsCRP), predicted forced expiratory volume in first second (FEV<sub>1</sub>%), Asthma Control Test (ACT) and mini Asthma Quality of Life Questionnaire (mAQLQ) were done in all patients before and after the study. Results were compared before and after study in each specific group, as well as between different groups.

**Sputum induction and processing:** Sputum was conducted concurrently with the inhaled hypertonic (3%) saline solution. Subjects were asked to rinse their mouth with water before the procedure to help eliminate squamous cell contamination of the sputum sample. They were asked to cough between each dose of nebulised saline to clear their throat and expectorate into a plastic Petri dish. This procedure continued until an adequate sample containing >0.5 ml visible mucocellular material was obtained. After induction, sputum was treated by adding four volumes of 0.1% dithiothreitol and rotated for 30 minutes at 37°C, followed by four volumes of phosphate buffered saline. The suspension was filtered through 60  $\mu$ m nylon gauze and then centrifuged at 200g for 10 minutes. Supernatant was aspirated and 70  $\mu$ l placed for slide preparation. The quality of induced sputum samples was assessed based on the presence of an adequate number of cells for enumeration, the presence of pulmonary macrophages on the slide, and the proportion of squamous epithelial cells. This gave a quality score ranging from 0 (poor quality) to 6 (good quality sample). A differential cell count was obtained by counting 400 non-squamous cells on slides fixed with methanol and stained with May Grunwald Giemsa. Eosinophils were enumerated as the percentage of 400 cells on slides fixed with methanol and stained with Chromotrope 2R. Metachromatic cells were counted as the percentage of 1500 cells on slides fixed in Carnoy's solution and stained with acidic toluidine blue.

Serum hsCRP levels were measured using a highly sensitive CRP assay (Behring Latex-Enhanced using the Behring Nephelometer BN-100; Behring Diagnostics, Westwood, MA, USA).

Peripheral blood relative eosinophil count was determined by an automated hematology analyzer (Cell-Dyn 4000; Abbott Laboratories, Abbott Park, IL).

**Spirometric tests:** Subjects withheld salbutamol 400  $\mu$ g for 20 minutes before testing. Height and weight were recorded before performing three reproducible forced expiratory manoeuvres wearing nose clips to measure forced expiratory volume in 1 second (FEV<sub>1</sub>) and vital capacity (VC).

**ACT test:** 5 questions assessing asthma symptoms (daytime and nocturnal), use of rescue medication, the effect of asthma on daily functioning and patient self-assessed level of control pertaining to the past 2-4 weeks. The total score range from 5-25: 20-25 are "well-controlled", 16-19 "not well-controlled" and 5-15 are "very poorly

controlled" asthma. The minimally important difference of the ACT is 3 points or more.<sup>4</sup>

Mini AQLQ: 15 questions in 4 domains (symptoms, activity limitation, emotional function and environmental stimuli), of which five items in the domain Symptoms, four items in the domain Activity Limitations, three items in the domain Emotional Function and three items in the domain Environmental Stimuli. Each question is rated on a 7-point scale (7=not impaired at all; 1=severely impaired). Change in mini AQLQ score of greater than 0.5 could be considered as clinically important.<sup>21</sup>

## Statistical analysis

Non-parametric and parametric methods are used to calculate statistical significance. Kolmogorov-Smirnov test and Shapiro-Wilk normality test were used in order to test the normality of distribution of variables. Mean values were shown as arithmetic mean  $\pm$  standard deviation in case of normal distribution of variables (age, BMI, hsCRP, FEV1 (%), or median [minimum value, maximum value] in case of non-normal distribution (sEo, bEo, ACT score and AQLQ

score). Two-sided student's t-test, Mann-Whitney test, Fisher's test and  $\chi^2$  test were used for calculating the difference between the groups. ANOVA test was used to calculate the relative difference distribution variance between variables. The statistical hypotheses were tested at the level of  $\alpha=0.05$ , and the difference between the groups in the sample was considered significant when  $p<0.05$  or less. Statistical significance was depicted as:  $p<0.05$ ,  $p<0.01$  and  $p<0.001$ . All data were analysed using GraphPad Prism version 7 (San Diego, California, USA).

## Results

150 non-smokers ( $47.41 \pm 11.85$  years, BMI  $23.9 \pm 1.78$  kg/m<sup>2</sup>, F/M ratio 1.05) with asthma treated by GINA 4 Step were included and divided into three groups according additional therapy: curcumin, placebo and control (without additional therapy) group. No adverse effects were observed during additional therapy. Age, gender and BMI showed similar distribution between curcumin, placebo and control group ( $p>0.05$ ) (Table 1). Also, before study sEo, bEo, hsCRP, FEV1 (% predicted), ACT score and AQLQ score were similar among groups ( $p>0.05$  for all measurements) (Table 1).

**Table 1** Baseline and follow up characteristics in curcumin, placebo and control group

Parameters	Curcumin group (n=50)	Placebo group (n=50)	Control group (n=50)	p value
Mean age (years)	48.24 $\pm$ 13.08	47.06 $\pm$ 11.44	46.94 $\pm$ 11.13	0.8339
Body mass index (kg/m <sup>2</sup> )	24.20 $\pm$ 0.76	23.59 $\pm$ 2.28	23.91 $\pm$ 1.92	0.2362
Females (n; %)	27 (54.0%)	22 (44.0%)	24 (48.0%)	0.6023
sEo (%)				
before study	5.5 [0, 47]	5 [0, 30]	5 [0, 39]	0.9165
after study	3 [0, 18]	5 [0, 21]	4 [0, 31]	0.0199*
p value	0.0019*	0.1846	0.4571	-
bEo (%)				
before study	5.9 [0.1, 15.3]	5 [0, 21]	5.55 [0.5, 16.9]	0.9647
after study	3.2 [0.1, 14.2]	5.55 [0.3, 17.3]	5.7 [0.4, 13.6]	0.038*
p value	0.0294*	0.7358	0.8332	-
hsCRP (mg/dl)				
before study	4.25 $\pm$ 1.93	3.81 $\pm$ 2.04	3.91 $\pm$ 2.03	0.3905
after study	2.9 $\pm$ 1.93	3.63 $\pm$ 1.77	3.57 $\pm$ 1.7	0.0402*
p value	0.0002*	0.6347	0.3699	-
FEV1 (%)				
before study	77.73 $\pm$ 5.61	75.98 $\pm$ 6.95	76.86 $\pm$ 7.11	0.2455
after study	86.02 $\pm$ 6.41	82.19 $\pm$ 9.07	82.14 $\pm$ 9.22	0.0309*
p value	< 0.0001*	0.0002*	0.0018*	-
ACT score				
before study	14.5 [6, 19]	13.5 [6, 20]	13 [6, 19]	0.973
after study	19 [8, 21]	16 [6, 20]	15.5 [6, 21]	0.0003*
p value	< 0.0001*	< 0.0001*	0.0008*	-
ACT change >3 after study (n; %)	29 (58.0%)	8 (16.0%)	8 (16.0%)	< 0.0001*
mAQLQ score				
before study	3 [2, 7]	3 [2, 7]	3 [2, 7]	0.8863
after study	5 [2, 7]	4 [1, 7]	4 [1, 7]	0.0114*
p value	< 0.0001*	0.016*	0.0032*	-
mAQLQ change $\geq$ 0.5 after study (n; %)	39 (78.0%)	25 (50.0%)	29 (58.0%)	0.0033*

(\*) difference was significant

After study, FEV1%, ACT and mAQLQ were higher in all groups than before study. In the same time, in curcumin group FEV1%, ACT and mAQLQ were higher than in placebo and control after study (Table 1).

Additionally, after study curcumin group showed lower sEo, bEo and hsCRP than before, while placebo and control group showed similar distribution of sEo, bEo and hsCRP before and after the study (Table 1).

Furthermore, curcumin group showed more frequent clinically significant improvement in ACT score (change>3) and in mAQLQ score (change $\geq$ 0.5) when compared to placebo and control after study (Table 1).

On the other side, despite of improvement in FEV1%, ACT and mAQLQ in placebo and control group after study, these parameters together with hsCRP, sEo and bEo were similarly distributed among placebo and control group (Table 1).

## Discussion

Over the years, there has been increasing evidence that curcumin, a phytochemical present in *Curcuma longa* (Turmeric or haldi), has a wide spectrum of therapeutic properties including modulation of inflammation and oxidative stress.<sup>10</sup> Many studies clearly established anti-inflammatory effects of curcumin, both in vitro and in vivo, by inhibiting iNOS production and scavenging the free radicals, inhibiting the activation of NF-kappaB and activating protein 1 (AP 1) and suppressing the production of proinflammatory cytokines.<sup>9</sup> Intranasal administration of curcumin significantly inhibited airway inflammation and pulmonary fibrosis in ovalbumin-induced chronic asthma, where MMP-9 activities were decreased along with  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), MMP-9, TIMP-1 and eotaxin expressions, suggesting that intranasal curcumin regulates airway inflammation and remodelling in chronic asthma.<sup>22</sup> In addition, data from various studies have demonstrated the efficacy of curcumin in animal models of asthma, but there are very few human trials, which explored the efficacy of oral curcumin in asthma with discordant results.<sup>10,23</sup> Our study was performed on 150 non-smokers with asthma treated by GINA 4 Step in order to analyse the impact of curcumin add-on therapy on inflammatory parameters, lung function, disease control and quality of life.

Curcumin, when used as a complementary treatment to albendazole, could help to alleviate eosinophilic meningitis through suppression of eosinophil count in the cerebrospinal fluid.<sup>24</sup> Exhibiting anti-inflammatory effects, curcumin improved total leukocyte count, erythrocyte sedimentation rate and blood eosinophils in asthma<sup>10</sup> and blood eosinophilia in a latex allergy model.<sup>25</sup> Furthermore, a significant reduction in various inflammatory markers such CRP was observed in patients with polycystic ovary syndrome,<sup>26</sup> osteoarthritis,<sup>27</sup> inflammatory bowel disease<sup>28</sup> and Crohn's disease<sup>29</sup> when treated with curcumin. Recent systematic review and meta-analysis of randomized controlled trials that were conducted to assess the influence of curcumin-containing supplements on biomarkers of inflammation and oxidative stress showed that curcumin supplementation significantly decreased interleukin 6 and high-sensitivity C-reactive protein.<sup>30</sup>

Moreover, curcumin coadministered with ovalbumin decreased airway constriction and hyperreactivity in sensitised guinea pigs.<sup>16</sup> In humans, curcumin-rich diet was significantly associated with better pulmonary

function, controlling for potential confounding by known risk factors for COPD. Increasing levels of curcumin intake were associated with higher mean adjusted FEV1 indicating a significant decrease in airway constriction and inflammation.<sup>31</sup> In mild to moderate asthma curcumin as add on therapy improved FEV1 values.<sup>10</sup>

Results from other studies are opposite. So, despite in vitro evidence that curcumin has anti-inflammatory properties and can inhibit allergic cytokine responses from lymphocytes in vitro, curcumin at 1000 mg twice daily supplementation did not significantly affect postbronchodilator FEV1, ACT scores, use of rescue bronchodilator, dose of inhaled corticosteroid, eNO levels, or levels of serum IgE, total white blood cells, antibody specific to Der p or Der f, and blood eosinophils in patients with moderate persistent atopic asthma (Kim 2011).<sup>20</sup> However, the number of patients in this study was very small (15 patients) and two in the treatment group dropped out, resulting in a very low statistical power of the study.

In our study in moderate to severe asthma patients curcumin group showed improvement in FEV1, ACT score, AQLQ score, sEo, bEo and hsCRP when compared to baseline levels as well as to placebo and control group. In addition, we observed more frequent clinically significant improvement in ACT score (>3) and AQLQ score ( $\geq$ 0.5) in curcumin group compared to both placebo and control group (Table 1). Our results are in concordance to majority of results of other authors indicating anti-inflammatory effects (sEo, bEo and hsCRP) and clinical benefits (FEV1, ACT and AQLQ score) of curcumin as add on therapy in step 4 asthma treatment.

On the other side, in the available and reviewed literature in English, we were unable to find a study that would compare the control (non-intervention) and placebo group. In our study FEV1%, ACT and mAQLQ, together with hsCRP, sEo and bEo were similarly distributed among placebo and control group after study (Table 1). These results could be point out the double confirmation of beneficial effects of curcumin comparing to both control and placebo group. However, despite the initially expected benefits of placebo, especially in ACT and AQLQ, effects of placebo were the same as that in the control group. This could be explained by the relatively short duration of our study. Perhaps a study that would include a longer period of time showed the differences between the placebo and the control group. In any case, these results create a realistic basis for the continuation of a similarly designed research.

Our study has some advantages and disadvantages. The advantages are: 1. the number of patients in groups is satisfactory, 2. the study is placebo-controlled and single-blinded, 3. up to our knowledge this is the first study in patients with moderate to severe asthma, who were not well controlled with standard therapy. The disadvantage is that the study has lasted 3 months only, so its results could not be valid for a long-term therapy.

In conclusion, add-on therapy with curcumin in patients with moderate to severe, partially controlled asthma seems to improve step 4 asthma treatment regarding lung function, disease control and quality of life. Future studies may benefit from a larger sample size, longer study duration, double blind design of the study, different dose of curcumin and/or improvements in oral bioavailability.

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the initial idea for the study. Jusufovic Azra and Halilovic Dzenan have recruited the patients. Kosnik Mitja, Arifhodzic Nermina and Sejdinovic Rifat were included in statistic processing of the data. Mona Al-Ahmad and Jasmina Nurkic have given valuable advices for sputum collection and its processing. Besides this during the writing of the study, all authors were included in collecting scientific material and analysing the results of the publication.

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**Competing interest:** None to declare

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