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EFFECTS OF CURCUMIN ON FUNCTIONAL CAPACITY AND PULMONARY FUNCTION IN CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS: A FEASIBILITY STUDY

EFEITO DA CURCUMINA NA CAPACIEDADE FUNCIONAL E NA FUNÇÃO PULMONAR EM CRIANÇAS E ADOLESCENTES COM FIBROSE CÍSTICA: UM ESTUDO DE VIABILIDADE

EFECTOS DE LA CURCUMINA EN LA CAPACIDAD FUNCIONAL Y LA FUNCIÓN PULMONAR EN NIÑOS Y ADOLESCENTES COM FIBROSIS QUÍSTICA: UM ESTUDIO DE VIABILIDAD

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ABSTRACT

This study aims to evaluate the efficacy of curcumin complexed with γ-cyclodextrin on pulmonary function and functional capacity in children and adolescents with Cystic Fibrosis (CF). A double-anonymized, randomized, placebo-controlled clinical trial was conducted involving children and adolescents with CF at a referral center. Over a 6-week period, the control group received a placebo while the intervention group received curcumin complex with γ-cyclodextrin (500 mg). Functional capacity was assessed using the 6-minute Walk Test (6MWT), and pulmonary function was evaluated through spirometry. The study enrolled eight patients (four adolescents in each group). The predominant mutation among the groups was heterozygous for ΔF508. There was no change in pulmonary function after the treatment period. The variation in 6MWT showed a trend of increase in the curcumin group (13.5%) compared to the control (8.3%), but it did not reach statistical significance. The preliminary results of this study demonstrated a relevant clinical impact on functional capacity measured by the 6MWT in favor of curcumin use in children and adolescents with CF.

Keywords: Cystic Fibrosis. Curcumin. Cystic Fibrosis Transmembrane Conductance Regulator. Walk Test. Respiratory Function Tests.

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RESUMO
Este estudo tem como objetivo avaliar o efeito da curcumina complexada com γ-ciclodextrina na função pulmonar e capacidade functional em crianças e adolescentes com Fibrose Cística (FC). Ensaio clínico placebo controlado, randomizado, duplo-anonimizado foi conduzido envolvendo crianças e adolescents com FC em um centro de referência. Durante 6 semanas o grupo controle recebeu placebo, enquanto o grupo intervenção recebeu curcumina complexada com γ-ciclodextrina (500 mg). A capacidade functional foi avaliada usando o Teste de Caminhada de 6 Minutos (TC6M) e a função pulmonar foi avaliada pela espirometria. O estudo envolveu oito pacientes (quatro adolescentes em cada grupo). A mutação predominante entre os grupos foi heterozigoto para ΔF508. Não houve mudança na função pulmonar após o período do tratamento. A variação no TC6M mostrou uma tendência de aumento no grupo curcumina (13.5%) comparado ao controle (8.3%), mas não alcançou significância estatística. Os resultados preliminares deste estudo demonstraram relevante impacto clínico da curcumina na capacidade functional em crianças e adolescentes com FC.

Palavras-chave: Fibrose Cística. Curcumina. Regulador da Conductância Transmembrana da Fibrose Cística. Teste de Caminhada. Testes de Função Respiratória.

RESUMEN
Este estudio tiene como objetivo evaluar el efecto de la curcumina complejada con γ-ciclodextrina en la función pulmonar y la capacidad funcional en niños y adolescentes con fibrosis quística (FC). Se llevó a cabo un ensayo clínico controlado con placebo, aleatorizado y doble ciego, que involucró a niños y adolescentes con FC en un centro de referencia. Durante 6 semanas, el grupo de control recibió placebo, mientras que el grupo de intervención recibió curcumina complejada con γ-ciclodextrina (500 mg). La capacidad funcional fue evaluada mediante la Prueba de Caminata de 6 Minutos (PC6M) y la función pulmonar fue evaluada por espirometría. El estudio incluyó a ocho pacientes (cuatro adolescentes en cada grupo). La mutación predominante entre los grupos fue heterocigoto para ΔF508. No se observaron cambios en la función pulmonar después del período de tratamiento. La variación en la PC6M mostró una tendencia a un aumento en el grupo de curcumina (13.5%) en comparación con el control (8.3%), pero no alcanzó significancia estadística. Los resultados preliminares de este estudio demostraron un impacto clínico relevante de la curcumina en la capacidad funcional en niños y adolescentes con FC.

Palabras clave: Fibrosis Quística. Curcumina. Regulador de la Conductancia Transmembrana de la Fibrosis Quística. Prueba de Caminata. Pruebas de Función Respiratoria.

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1 INTRODUCTION

Cystic Fibrosis (CF) is a lethal autosomal recessive genetic disease in which pulmonary impairment accounts for 80% of mortality in affected individuals (Flume et al., 2007). Therapies aimed at modulating and restoring the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein have been developed in recent decades. Curcumin, a bioactive compound with potential therapeutic properties including anti-inflammatory, antioxidant, and immunomodulatory effects, has been the subject of molecular studies targeting CFTR protein and the correction of its functional defects (Egan et al., 2004; Song et al., 2004; Grubb et al., 2006).

Although in vitro studies have demonstrated potential for varying degrees of restoration of CFTR function (Egan et al., 2004; Bellachio, 2023), only two studies have evaluated the clinical effect of curcumin in individuals with CF (Berkers et al., 2020; Talebi et al., 2021). Its poor absorption and rapid metabolism (Anand et al., 2007) have limited its clinical use. Complexing curcumin with cyclodextrins is an alternative to improve its absorption, as these complexes can enhance aqueous solubility and intestinal absorption of active compounds (Alonso et al., 2016).

Purpura et al. (Purpura et al., 2018) compared the oral bioavailability of different commercial products containing curcumin in humans. Among the evaluated products, the curcumin complex with γ-cyclodextrin showed the highest relative bioavailability gain (approximately 40 times compared to unformulated curcumin extract administration), highlighting its potential to enhance the biopharmaceutical properties and clinical effects of curcumin.

Among the clinical effects, the evaluation of functional capacity using the 6-minute Walk Test (6MWT) holds valuable utility as a prognostic marker for hospitalization and risk of death in moderate to severe lung diseases (ATS, 2002; Agarwala; Salzman, 2020). Studies investigating CFTR potentiators often use the 6MWT to assess functional capacity; however, the effect of curcumin on the 6MWT in individuals with CF has yet to be documented in the literature.

This study aimed to evaluate the efficacy of curcumin on pulmonary function and functional capacity in children and adolescents with CF.

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2 MATERIALS AND METHODS

2.1 STUDY DESIGN

This study is a double-blind, placebo-controlled, randomized clinical trial conducted with children and adolescents diagnosed with CF at a specialized hospital in the central-west region of Brazil. The Research Ethics Committee approved the research protocol (approval number 3.256.001), registered in the Brazilian Clinical Trials Registry (ReBEC—RBR-8gmn4w).

For sample size calculation, a 95% confidence interval and 80% power were used, based on a percentage reduction of IL-6 of 61% in the treatment group and 16% in the control group, as reported in the study by Panahi et al. (PANAHI et al., 2015). This calculation determined a sample size of 36 participants, with 18 individuals assigned to the intervention group and 18 to the control group. Using the software available at www.randomization.com, the numbers were randomly assigned to enter the study.

The inclusion criteria for this study were age between 5 and 18 years, confirmed diagnosis of CF with two sweat tests greater than or equal to 60 mmol/L, and/or two pathogenic CF mutations. Exclusion criteria included children under four years old and those with forced expiratory volume in one second (FEV1%) ≤ 40% of predicted.

2.2 STUDY INTERVENTION

The intervention group received 500 mg of curcumin (dry extract from the rhizomes of Curcuma longa L, > 65% w/w curcumin, Sigma-Aldrich Brasil Ltda, São Paulo) complexed with γ-cyclodextrin (Cavamax W8®, Ashland Inc., São Paulo). The inclusion complex was prepared by mixing an ethanolic solution of curcumin (1% w/w) with an aqueous solution of γ-cyclodextrin (21.6% w/w) under mechanical stirring for 2h. The mixture was then dried under forced air circulation. The dried material was mixed with microcrystalline cellulose (Avicel pH 101, FMC, Germany) and encapsulated in hard gelatin capsules (0.68 mL each) under controlled conditions. All handling was performed following current sanitary recommendations (BRASIL, 2007) at the University Pharmacy of the Federal University of Goiás.

The control group used hard gelatin capsules containing only microcrystalline cellulose, which had the same physical characteristics as the curcumin capsules. Both groups were instructed to orally ingest two capsules during lunch and dinner for six weeks.

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2.3 OUTCOMES

Pulmonary function was assessed using the KoKo Spirometer (Koko® Spirometer, PDSInstrumentation, Louisville, CO, USA). Spirometry was conducted following the guidelines of the American Thoracic Society and the European Respiratory Society for children (ATS, 2002). The spirometry parameters evaluated were: Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1%), Tiffeneau Index (FEV1/FVC ratio), and Forced Expiratory Flow between 25% and 75% of FVC (FEF25-75%), both before and after administration of 4 puffs of 100 mcg salbutamol.

Functional capacity was assessed using the 6-minute Walk Test (6MWT), following the American Thoracic Society (ATS, 2002) guidelines. Parameters evaluated before and after the test included heart rate (HR), oxygen saturation (SpO2) measured with a pulse oximeter, blood pressure, respiratory rate (RR) (counted by chest wall excursions per minute), and the Modified Borg Scale score to measure perceived dyspnea intensity.

Patients were instructed to walk as far as possible for six minutes in a 30-meter hallway on a flat, hard surface marked every meter. The predicted distance for each participant was calculated based on age, height, and weight, using the formula derived from the Brazilian study by Priesnitz et al. (2009).

The anthropometric profile of children and adolescents was assessed based on weight, height, and appropriate anthropometric indicators for their age group. The values were expressed as mean z-scores, using the World Health Organization growth curves as a reference (WHO, 2006).

2.4 STATISTICAL ANALYSIS

Data were tabulated in a Microsoft Excel spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS, version 22.0). Numerical variables were presented as frequency and mean ± standard deviation, while categorical variables were expressed as absolute frequency and percentage. Pearson's Chi-Square or Fisher Freeman-Halton Exact test was applied to analyze categorical variables. The Kolmogorov-Smirnov test was used to assess the distribution of numerical variables. For within-group comparisons, paired T-test was used for parametric variables and Wilcoxon test for non-parametric variables. Between-group

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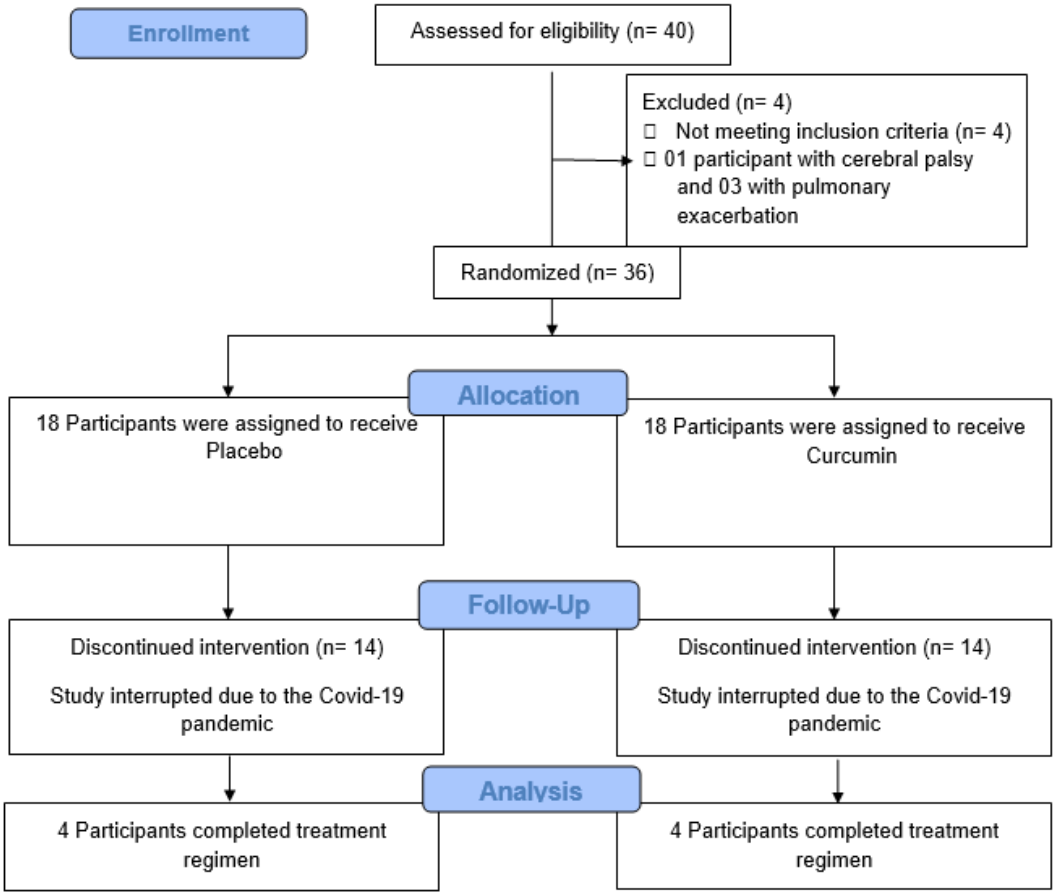
comparisons utilized the Student's T-test or the Mann-Whitney test, depending on the variable distribution. The significance level was set at 5% ($p < 0.05$).

3 RESULTS

Eight participants were enrolled in this feasibility study within the available data collection time, with 4 participants allocated to each treatment regimen (Figure 1).

Figure 1

Participant disposition according to the CONSORT diagram



The pre-intervention parameters of the curcumin and control groups for clinical and anthropometric data are presented in Table 1. The groups were homogeneous in terms of initial sociodemographic characteristics. The predominant mutation in both groups was heterozygous for ΔF508 (62.5%). The groups were not homogeneous regarding the

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variables Tiffeneau Index (FEV1/FVC ratio), FEF25-75%, and predicted value of the 6-minute Walk Test (6MWT).

Table 1

Clinical, anthropometric, pulmonary function, and functional capacity characteristics of the curcumin and control groups before intervention.

Characteristics	Curcumin (n=4) Mean ± SD n (%)	Control (n=4) Mean ± SD n (%)	p-value
Age	10,81 ± 1,75	13,66 ± 3,12	0.157*
Sex			
Male	3 (75,0)	1 (25,0)	0.480#
Female	1 (25,0)	3 (75,0)	
Ethnicity			
White	0 (0)	3 (75,0)	0.144#
Mixed race	4 (100)	1 (25,0)	
Age at diagnosis (months)	6 ± 3,6	6 ± 3,9	1.000*
Genetic mutations			
Homozigoto ΔF508	0 (0)	1 (25,0)	0.452§
Heterozigoto ΔF508	3 (75,0)	2 (50,0)	
No ΔF508	1 (25,0)	1 (25,0)	
Diagnosis			
Neonatal screening	1 (25,0)	2 (50,0)	0.462#
Clinical symptoms	3 (75,0)	2 (50,0)	
Shwachman-Kulczyck score			
Moderate	0 (0)	1 (25,0)	0.261#
Mild	0 (0)	1 (25,0)	
Good	2 (50,0)	2 (50,0)	
Excellent	2 (50,0)	0 (0)	
P. aeruginosa colonization			
Yes	3 (75,0)	3 (75,0)	1.000#
No	1 (25,0)	1 (25,0)	
Anthropometry			
Height (m)	1,37 ± 0,05	1,55 ± 0,12	0.053*
Height for age z-escore	- 0.83 ± 0,98	0,23 ± 0,69	0.134*
BMI (kg/m^2)	20,54 ± 4,90	16,45 ± 3,03	0.215*
BMI for age z-escore	0,93 ± 1,82	-1,32 ± 0,94	0.085*
Pulmonary function			
FEF 25-75%	75,00 ± 9,64	33,00 ± 26,05	**0.013***
VEF1%	83,50 ± 7,55	51,50 ± 25,17	0.081°
CVF	85,33 ± 8,38	69,00 ± 26,88	0.143*
Tiffenau	85,67 ± 6,02	69,00 ± 6,55	**0.005***
Functional capacity			
Predicted 6-minute Walk Test (m)	582,83 ± 30,20	640,58 + 26,99	**0.025***
6-minute Walk Test (m)	471,73 ± 62,66	527,24 + 48,92	0.429*
Percentage of predicted 6-minute walk distance	80,75 ± 9,21	82,67 + 10,40	0.738*

Height-for-age (H/A); BMI: body mass index; BMI-for-age z-score: BMI z-score for age; FEF 25-75%: forced expiratory flow between 25% and 75%; VEF1%: forced expiratory volume in 1 second as a percentage of predicted value (FEV1%); FVC: forced vital capacity; TC6M: 6-minute walk test. *Student's t-test; # Fisher's exact test; § Freeman-Halton exact test; ° Mann-Whitney test.

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There was no significant difference between the groups in terms of pulmonary function. Following the intervention, the curcumin group showed a mean increase of 69.63 meters in the 6-minute Walk Test (6MWT) compared to the baseline. The control group exhibited an increase of 59.45 meters from pre-intervention values. Additionally, in the curcumin group, the percentage change in distance walked relative to predicted values increased by 13.50%, while in the control group, it increased by 8.33%. However, no significant intra-group differences were detected in the assessment. Post-intervention differences were significant in height and predicted 6MWT values (Table 2).

No exacerbations occurred during the intervention, and there were no adverse events or atypical gastrointestinal or systemic manifestations related to the treatment regimens used.

Table 2

Changes post-intervention in anthropometry, pulmonary function, and functional capacity in the curcumin and control groups.

	Curcumin			Control			
	Pre-intervention	**Post-intervention**	**p-value[1]**	**Pre-intervention**	**Post-intervention**	**p-value[1]**	**p-value[2]**
Anthropometry Weight (kg)	39,2 ± 10,5	40,57 ± 10,71	0.057#	40,9 ± 13,9	42,12 ± 14,17	0.095#	0.868*
Height (m)	1,37 ± 0,05	1,37 ± 0,05	0.391#	1,55 ± 0,12	1,56 ± 0,12	0.252#	**0.046***
BMI (kg/m^2)	20,54 ± 4,90	21,20 ± 4,55	0.129#	16,45 ± 3,03	16,77 ± 3,04	0.238#	0.164*
H/A z-escore	- 0.83 ± 0,98	- 0,90 ± 0,99	0.127#	0,23 ± 0,69	0,31 ± 0,72	0.485#	0.101*
BMI/A z-escore	0,93 ± 1,82	1,15 ± 1,55	0.237#	-1,32 ± 0,94	- 1,16 + 0,90	0.369#	0.051*
Pulmonary function							
FEF $_{25-75\%}$	75,00 ± 9,64	74,25 ± 17,17	0.469#	33,00 ± 26,05	36,25 ± 32,04	0.342#	0.096*
VEF1%	83,50 ± 7,55	81,75 ± 19,27	0.715§	51,50 ± 25,17	54,50 ± 31,22	0.414§	0.198°
CVF	85,33 ± 8,38	86,00 ± 21,21	0.843#	69,00 ± 26,88	66,75 + 27,54	0.224#	0.313*
Tiffenau	85,67 ± 6,02	82,25 ± 6,89	0.122#	69,00 ± 6,55	71,50 ± 8,37	0.367#	0.104*
Functional capacity							
Predicted 6-minute Walk Test (m)	582,83 ± 30,20	576,22 ± 32,33	0.189#	640,58 ± 26,99	646,59 ± 24,42	0.265#	**0.022***
6-minute Walk Test (m)	471,73 ± 62,66	541,37 ± 62,40	0.187#	527,24 ± 48,92	586,70 ± 2,25	0.180#	0.242*
% covered	80,75 ± 9,21	94,25 ± 12,14	0.151#	82,67 ± 10,40	91,00 ± 3,60	0.251#	0.642*
Δ 6MWT (m)	69,63 ± 81,65			59,45 ± 50,53			0.848*
Δ 6MWT % covered	13,50 ± 14,05			8,33 ± 9,01			0.581*

Weight-for-age (W/A); Height-for-age (H/A); BMI: body mass index; BMI-for-age z-score: BMI z-score for age; FEF 25-75%: forced expiratory flow between 25% and 75%; VEF1%: forced expiratory volume in 1 second as a percentage of predicted value (FEV1%); FVC: forced vital capacity; TC6M: 6-minute walk test; Δ TC6M: change in meters between pre- and post-intervention TC6M; ΔTC6M %percorrido: percentage change in distance covered between pre- and post-intervention TC6M. #Student's t-test; #Paired t-test; §Wilcoxon signed-

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rank test; *Student's t-test; °Mann-Whitney test. 1Intragroup pre- and post-intervention comparison; 2Post-intervention comparison between groups.

4 DISCUSSION

The preliminary results of this feasibility study showed favorable outcomes regarding increased walking distance in the 6-minute walk test (6MWT), suggesting that curcumin may improve functional capacity in children and adolescents with CF. However, the proposed intervention did not modify pulmonary function.

The 6MWT is considered a biomarker of everyday functional capacity, assessing the integrated submaximal response of the cardiovascular, neuromuscular, peripheral circulation, and muscular metabolism systems. It aims to measure the response to therapeutic interventions in severe cardiac or pulmonary diseases (GUR et al., 2019). It has been used as a predictor of morbidity and mortality and as a prognostic marker of severity in pulmonary diseases (TOOPCHIZADEH et al., 2023).

Determined the minimal clinically detectable change (MDC) capable of producing a positive clinical effect on walking distance in children and adolescents with CF, suggesting improved exercise tolerance and favorable clinical response with the proposed therapy. For children, the MDC within a 90-95% confidence interval ranged from 59.39 - 70.55 meters, and for adolescents, from 47.81-56.8 meters. In our study, the curcumin group walked greater distances than the control group after treatment, with a mean difference (69.63 - 81.65) exceeding the MDC for adolescents (47.81 - 56.8 meters) suggested by the authors. The achieved distance by the curcumin group was 13.50% of the predicted value compared to 8.33% in the control group.

Our study's results with curcumin are similar to those obtained with other potentiators and modulators of CFTR action. After four weeks of Lumacaftor/Ivacaftor use in homozygous ΔF508 adults, the increase in 6MWT distance was 74 meters (TERLIZZI et al., 2021). In another study, three ΔF508 mutation carriers also showed increased 6MWT distances (198 meters, 77 meters, and 44 meters for subjects 1, 2, and 3, respectively) after eight weeks of Elexacaftor/Tezacaftor/Ivacaftor combination use (WARK et al., 2019).

To our knowledge, our study is the first to evaluate the effect of curcumin on functional capacity parameters in CF individuals (HEIDARI, 2022). Well-established evidence regarding curcumin use and improved 6MWT performance is found in individuals with osteoarthritis. This bioactive compound can reduce pain and increase physical performance,

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with doses ranging from 80 to 2000 mg/day and treatment durations from 4 weeks to 8 months (PAULTRE et al., 2021; WANG et al., 2021; LOPRESTI et al., 2021).

In our study, there was no clinical change in lung function. The supplementation period implemented during the COVID-19 pandemic (6 weeks) may have been insufficient. CFTR modulator studies have shown that significant changes in forced expiratory volume in one second (FEV1%) are detectable only after 8 to 12 weeks of intervention using spirometry. Consistent with these findings, Berkers et al. (2020) did not find a significant clinical response in FEV1% with combined curcumin and genistein supplementation for 8 weeks in adolescents and adults expressing the S1251N mutation.

Limitations regarding the study's development need to be addressed, with sample size being the most significant. The study began before the COVID-19 pandemic, making it impossible to provide in-person patient care at the Cystic Fibrosis Outpatient Clinic until the end of 2020, resulting in a suspension of data collection. Secondly, the lack of laboratory analysis of anti- and pro-inflammatory cytokine behavior after curcumin supplementation due to the suspension of in-person visits prevented us from evaluating the serum response of these markers in our sample.

On the other hand, administering a curcumin complex with γ-cyclodextrin to CF patients is novel, and functional test results suggest that the absorption level of the active compound was sufficient to result in performance gains in patients.

5 CONCLUSION

The study results showed a favorable signal for a clinical impact on functional capacity measured by the 6MW with the use of curcumin in children and adolescents with CF, underscoring the importance of disseminating these findings as preliminary results of a clinical trial. However, pulmonary function did not change during the 6-week treatment period.

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