Effects of curcumin on cystic fibrosis: a systematic review protocol

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Protocol

Keywords: cystic fibrosis, cystic fibrosis transmembrane conductance regulator, chloride channels, curcuma, curcumin

Posted Date: September 16th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-889593/v1

Abstract

Background: Cystic Fibrosis is a genetic disease characterized by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, responsible for encoding the protein that regulates the function of chlorine and sodium channels in the cell membrane. The bioactive compound curcumin has shown modulating and restorative effects on sodium, chlorine and water transport, and seems to be a candidate to act in the expression of the function of the chlorine channels. The purpose of this protocol is to demonstrate scientific evidence of molecular and clinical effects of curcumin in cell cultures, animals and subjects with cystic fibrosis.

Methods: The search will be conducted in the following databases - MEDLINE/PubMed, SCOPUS, Cochrane Library and EMBASE. Reviewers will select original intervention (in vitro and in vivo) and/or observational articles that analyzed the effects of curcumin on cystic fibrosis. The methodological quality of the studies will be assessed by the Joana Briggs Institute's Checklist for Quasi-Experimental Studies. The GRADE tool will be applied to grade the quality of evidence.

Discussion: To date, no systematic reviews have been published that assessed molecular and clinical effects of curcumin on cystic fibrosis. Upon completion of this systematic review, it is expected that the evidence found may contribute to the development of therapeutic formulations capable of modulating the function of the CFTR protein, restoring its properties, and contributing to the reduction of systemic clinical manifestations of cystic fibrosis.

Systematic review registration: PROSPERO CRD42021229294

Background

Cystic fibrosis (CF) is an autosomal recessive genetic disorder characterized by a mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, responsible for encoding the protein that regulates the conductance of chlorine channels in the cell membrane [1]. Mutant CFTR is synthesized within the endoplasmic reticulum membrane, but fails to adequately perform its function, being directed to degradation via the Golgi complex [2].

Currently, more than 2,000 CFTR mutations have been identified, which are categorized into six classes, depending on the existing effect on CFTR expression or function [3]. Defects can occur from the folding and transit of the CFTR protein, to the opening of the chloride channel and thermal stability at the apex of the cell surface [4].

As a consequence, there is a reduction in chloride secretion to the luminal surface, with an increase in sodium absorption, compromising ion transport and mucociliary clearance in target organs such as the lung and the gastrointestinal tract [5].

In the lungs, the mucus becomes thick and sticky leading to increase in the inflammatory response and the recurrence of airway infections. Thus, pulmonary structural damage is perpetuated cyclic and continuously [6]. In the gastrointestinal tract, the main manifestations are secondary to pancreatic insufficiency. The mucus obstructs the pancreatic ducts impairing the secretion of enzymes into the duodenum, causing poor digestion of fats, proteins, and carbohydrates [7].

Over the years, the treatment of CF has been based on the improvement of symptoms and clinical manifestations, such as replacement of pancreatic enzymes, use of antibiotics in infections and mucolytics in pulmonary disease [8]. However, in recent decades, the study of nutraceutical agents capable of repairing the functions of chloride channels, through the action on the CFTR gene, has attracted attention in clinical practice [9].

Current evidence suggests that curcumin, a natural bioactive compound present in the root of the *Curcuma longa L* plant, may restore normal transport in chloride channels through activation, potentiation, or rescue of the functions of this channel [10, 11, 12].

Curcumin acts as an inhibitor of the sarcoplasmic/endoplasmic reticulum Ca2 + pump (SERCA). This action reduces the calcium concentration in the lumen of the endoplasmic reticulum and allows the CFTR to achieve its cell surface functionality [2].

Egan and coworkers, in 2004 [13], reported an improvement in the survival of mice transfected with the ΔF508-CFTR mutation that used curcumin. Their findings demonstrated that curcumin was able to induce the functional expression of the chloride channel on the surface of the plasma membrane. However, other studies did not obtain similar results when reproducing the methodology used in that experiment [12, 14, 15].

Faced with conflicting results, it is important to elucidate whether the in vitro effect of curcumin on CFTR may reflect on the functionality of this protein in vivo, and, consequently, on the improvement of clinical parameters. Thus, the purpose of this protocol is to critically assess the scientific evidence of the effects of curcumin on CFTR function and clinical outcomes in CF.

Methods/design

The development of this protocol followed the recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 (PRISMA-P 2015) [16] (Additional File 1). The preparation of this systematic review will follow the steps described in this protocol; if eventual changes are necessary, they will be properly reported and justified. This systematic review protocol is registered in the International Prospective Register of Systematic Review (PROSPERO) with registration number CRD42021229294. Registration related information can be accessed at http://www.crd.york.ac.uk/PROSPERO.

Research question

Is the use of curcumin able to improve CFTR function and clinical outcomes in CF?

Eligibility criteria

Type os study

Observational, experimental (in vitro), and/or interventional (in vivo) original articles will be included, without date and language restrictions. Case reports, letters to the editor and narrative reviews will be excluded.

Participants

The studies should characterize the participants as follows: 1) humans with CF, regardless of gender and age; 2) animal models transfected with any type of CF mutation and 3) cell cultures (in vitro) originating from individuals homozygous or heterozygous for any CF mutation.

Intervention

Studies that used curcumin (alone or in combination) will be included, regardless of the formulations presented (extract, capsule, or powder), in order to promote better expression of CFTR in different gene mutations that compromise its functions.

Comparator

Studies should demonstrate that comparisons have been made between the therapeutic effect of curcumin with other bioactive compounds or placebo.

Outcomes

Outcomes that demonstrate changes in CFTR maturation, expression, and function after exposure to curcumin, with the consequent restoration of chloride transport across the cell membrane will be considered.

Search strategy

Electronic databases

Two researchers will search the studies in the following databases: PubMed–MEDLINE (www.ncbi.nlm.nih.gov/pubmed/), EMBASE (www.embase.com), Cochrane Library (www.cochranelibrary.com), PROSPERO (www.crd.york.ac.uk), SCOPUS (https://www.scopus.com). As a search strategy, descriptors suitable for the research question will be identified from the controlled vocabularies of the Medical Subjects Heading (MeSH) and between terms. The descriptors will be combined using Boolean operators and used to identify the studies of interest. Figure 1 exemplifies the search strategy used in the PubMed database – MEDLINE, which will be replicated in the other databases (Additional File 2).

Selections of studies

The Mendeley reference manager software will be used to tabulate studies and select duplicates. Two independent reviewers (IZA and GMA) will select the studies found by the two-phase search strategy:

Phase 1: screening of titles and abstracts

Reviewers will assess whether selected titles and abstracts meet predetermined eligibility criteria.

Phase 2: screening of articles after reading the full text

The articles selected after reading the titles and abstracts will be read in full and re-analyzed for eligibility criteria. In case of disagreement between reviewers, a third reviewer will be consulted (PSSC).

The selected studies will submit qualitative assessment and data extraction. For a better visualization of the steps related to the selection of studies, the diagram proposed by PRISMA (Preferential Reporting Items for Systematic Reviews and Meta-analyses) will be presented [17].

Extraction of data

A table will be created in Microsoft Word® (Microsoft Corporation), specifically for the purpose of this review, where the following data will be extracted and tabulated: (1) author, country and year of publication; (2) study design and population characteristics – age, type of genetic mutation, cell lineage; (3) study objectives; (4) intervention – doses of curcumin used, time of exposure to treatment and/or incubation; (5) outcomes - changes in chloride efflux and transport, movement of CFTR towards the plasma membrane, restoration of CFTR expression, change in chloride channel opening time and its functionality, and correction of the nasal potential difference defect.

Assessment of methodological quality

Risk of bias

The risk of bias analysis will be performed using the checklist for Quasi-Experimental Studies, prepared by the Joana Briggs Institute, and recommended by Tran et al., 2021 [18]. The objective of this tool will be to assess the methodological quality of the studies, determining whether the possibility of bias in their design, conduct, and analysis was addressed [19]. This tool contains nine criteria to be judged among: "yes", when the item was correctly reported, "no", when the item was not reported, "not clear", when it is not clear whether the item was reported, and "no applicable", When is not applicable report the information requested in the item (Additional File 3). The final score will be the number of “yes” scored divided by the maximum score (9) and multiplied by 100.

Assessment of the quality of evidence – GRADE Cochrane

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool will be applied to grade the analysis of the quality of evidence and the strength of the recommendations. Five criteria will be evaluated: 1. methodological limitations (risk of bias); 2. inconsistency (heterogeneity); 3. indirect evidence; 4. imprecision; and 5. publication bias. For each item, a category should be applied: (a) high - we are very confident that the true effect is close to the effect estimate; (b) moderate - we are moderately confident in the effect estimate, and the true effect will likely be close to the effect estimate, but there is a possibility that it will be substantially different; (c) low - our confidence in the effect estimate is limited and the true effect may be substantially different from the effect estimate and (d) very low - we have very little confidence in the effect estimate and the true effect [20].

The methodological evaluation and quality of evidence will be analyzed independently by two researchers (IZA and PMF). If there is disagreement, a third reviewer will be consulted (PSSC).

Data synthesis

A qualitative summary of the evaluation of variables, interventions, outcomes, and any other information relevant to the objectives proposed by the review will be reported in the form of tables or narratives. If appropriate, the characteristics of the variables will be submitted to statistical analysis.

Discussion

This systematic review will synthesize current scientific evidence on the molecular and clinical effects of curcumin in cell cultures, animals, and humans with CF. To our knowledge, this synthesis has not yet been carried out. This study proposal may suffer some limitations: first, due to the characteristics of the selected studies, which are, for the most part, in vitro, which allows us to make only preclinical inferences. The insufficient number of randomized controlled trials may affect the robustness of the findings; second, the methodological quality of the studies can make data extrapolation difficult, and finally, the methodological heterogeneity of the studies can be a challenge in the joint interpretation of the results.

The findings of this systematic review will be valuable in directing the development of therapeutic formulations that can modulate the function of the CFTR protein, restoring the properties of chloride channels in fluidizing mucus in target organs and contributing to the reduction of systemic clinical manifestations of CF. Furthermore, currently existing treatments are only available to a small part of CF patients worldwide.

List Of Abbreviations

CF: Cystif Fibrosis; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MeSH: Medical Subjects Heading; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-analysis–Protocol.

Declarations

Authors' contributions

All authors, IZA, GMA, PMF, LDCC and PSSC, were involved in the intelectual production and protocol design. The steps of searching, extracting, and synthesizing data proposed in the protocol will be developed by the authors IZA, GMA and PMF under the coordination of LDCC and PSSC. At the end of the development of the steps described in the protocol, the authors IZA, GMA, PMF, LDCC and PSSC will carry out the analysis, interpretation, and discussion of the results for the production of the systematic reviews. The reviewers IZA and PSC were responsible for writing the protocol. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

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Figures

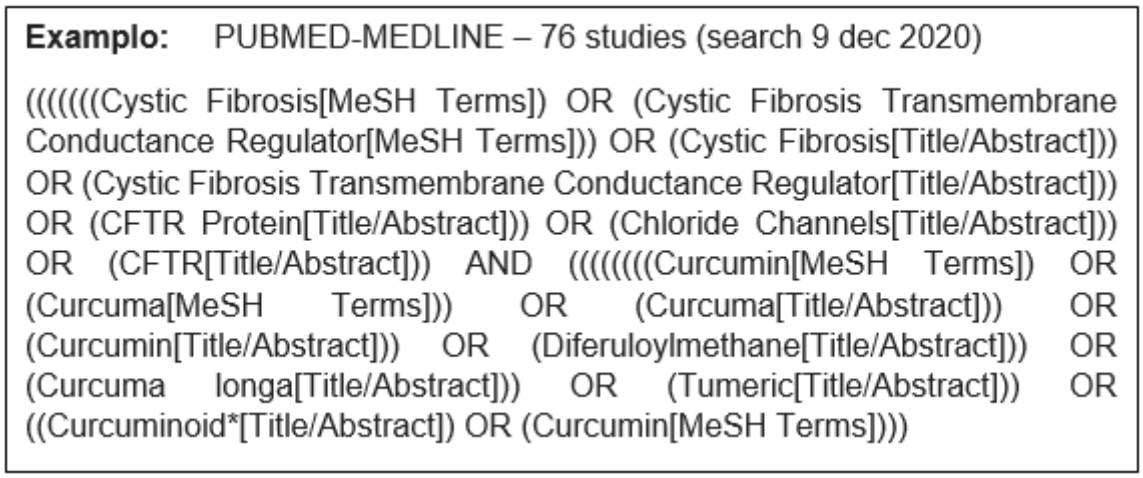

Figure 1

Combination of keywords and entry terms for search in the database.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1PRISMAP2015checklist.docx
- AdditionalFile2PubMedSearch.docx
- AdditionalFile3JBIChecklist.docx