DOI: 10.53660/CLM-3539-24L33

Effects of curcumin on cystic fibrosis: a systematic review

Efeitos da curcumina na fibrose cística: uma revisão sistemática

Received: 21-04-2024 | Accepted: 25-05-2024 | Published: 31-05-2024

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ABSTRACT

The evidence that curcumin has restorative effects on the chlorine channels function is contradictory in the literature. This systematic review summarizes of molecular and clinical effects of curcumin related to cystic fibrosis (CF). Three databases were searched, where the outcome was the maturation, transport, expression and functionality of cystic fibrosis trasmennrane regulator (CFTR). Were included studies in vitro and in vivo that compared curcumin supplementation with other bioactive compounds or placebo. Of the 19 studies included, 18 were in vitro and 1 was a randomized clinical trial, with low-moderate risk of bias. Curcumin seems to be related to genetic mutations that lead to a defect in the opening of the chloride and sodium channel, allowing the repair of the functionality of this protein. The effect in inducing CFTR maturation and the expression of its function on the cell surface, are conflicting. The use of curcumin in CF patients is incipient and does not allow clinical inferences. PROSPERO CRD42021229294.

Keywords: Cystic fibrosis; Cystic fibrosis transmembrane conductance regulator; Curcumin.

RESUMO

A evidência de que a curcumina tem efeitos restauradores na função dos canais de cloro é contraditória na literatura. Esta revisão sistemática resume os efeitos moleculares e clínicos da curcumina relacionados à fibrose cística (FC). Foram pesquisadas três bases de dados, onde o resultado foi a maturação, transporte, expressão e funcionalidade do regulador transmenano da fibrose cística (CFTR). Foram incluídos estudos in vitro e in vivo que compararam a suplementação de curcumina com outros compostos bioativos ou placebo. Dos 19 estudos incluídos, 18 foram in vitro e 1 foi um ensaio clínico randomizado, com risco de viés baixo a moderado. A curcumina parece estar relacionada com mutações genéticas que levam a um defeito na abertura do canal de cloreto e sódio, permitindo a reparação da funcionalidade desta proteína. O efeito na indução da maturação do CFTR e a expressão da sua função na superfície celular são conflitantes. O uso da curcumina em pacientes com FC é incipiente e não permite inferências clínicas.

Palavras-chave: Fibrose cística; Regulador de condutância transmembrana em fibrose cística; Curcumina.

INTRODUÇÃO

Cystic Fibrosis (CF) is an autosomal recessive disease caused by a mutation in the gene that encodes the transmembrane conductance regulatory protein (CFTR) (REN et al., 2018). CFTR functions as a phosphorylation-dependent, cyclic AMP-regulated chlorine channel. CFTR functions as a phosphorylation-dependent, cyclic AMP-regulated chlorine channel. The different mutations that can occur in CFTR may be associated with specific CF phenotypes and interfere with the pathophysiology of the disease (CUTTING, 2015).

Traditionally, treatment for CF was based on respiratory symptoms, in terms of fighting lung infections and inflammation resulting from excess mucus produced, and on enzyme replacement in situations of pancreatic insufficiency (FARREL; ROCK; BAKER, 2020). However, over the years, knowledge of the pathophysiology of the disease has contributed to early diagnosis and provided advances in treatment from therapeutic strategies that modulate the function of the CFTR gene (SCOTET; L'HOSTIS; FÉREC, 2020).

Six classes of CFTR mutations can occur, influencing the expression and function of this protein. Changes can occur in the folding and CFTR traffic in the cell, at the opening of the channel, on thermal instability at the cell surface, and on channel activity itself (DEKER et al., 2016). The development of CFTR modulators that can restore mutant chlorine channel function has been studied in recent decades for use in clinical practice (REN et al., 2018).

Curcumin, the primary bioactive compound present in the root of the plant *Curcuma Longa L*, has been studied in recent decades for its property of lowering calcium levels in the endoplasmic reticulum, preventing chaperone proteins from trapping poorly processed CFTR and directing it to degradation (ZEITLIN, 2004). Egan et al. (2004), pioneer researchers of this theory, demonstrated that curcumin promoted the escape of CFTR to the cell surface, restoring the function of the chloride channel. However, other authors who have explored this curcumin-mediated phenomenon have not reported evidence that this dietary supplement can correct CFTR-related defects (SONG et al., 2004; GRUBB et al., 2006).

The purpose of this review was to critically analyze the primary evidence regarding the use of curcumin as a therapeutic strategy to correct the defect in CFTR processing, function, and expression, and to assess whether the in vitro effects of curcumin can reflect on the functionality of this protein in vivo and, consequently, in the improvement of clinical parameters.

MATERIALS AND METHODS

Protocol and registration, reporting

This systematic review was registered with PROSPERO under registration number CRD42021229294. Reporting has been conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PAGE et al., 2021).

Research question

Does the use of curcumin correct the defect in CFTR processing, function, and expression, reflecting on the functionality of this protein in vivo and, consequently, in the improvement of clinical parameters?

Elegibility criteria

Observational, experimental (in vitro), and interventional (in vivo) original articles were considered eligible, with no specific range of date of publication and language restrictions. Case reports, letters to the editor, and narrative reviews were excluded. We determined eligibility based on the PICO of trials in the following manner:

P – Population – we included studies that characterized the participants as follows: 1) humans with CF, regardless of gender and age; 2) animal models transfected with any CF mutation and 3) cell cultures (in vitro) originating from individuals homozygous or heterozygous for any CF mutation.

I – Intervention – studies that used curcumin (alone or in combination) were included, regardless of the formulations presented (extract, capsule, or powder), to promote better expression of CFTR in different gene mutations that compromise its functions.

C – Comparator – we included studies that demonstrated comparisons between the therapeutic effect of curcumin with other bioactive compounds or placebo.

O – Outcomes – our primary interests were outcomes that demonstrated positive effects in chloride efflux and transport, movement of CFTR towards the plasma membrane, restoration of CFTR expression, improvement in chloride channel opening time and its functionality, and correction of the nasal potential difference defect.

Systematic search and selection

We conducted the systematic search using the same search key as detailed in supplementary material Suppl1. for three databases: PubMed–MEDLINE (www.ncbi.nlm.nih.gov/pubmed/), EMBASE (www.embase.com), SCOPUS (https://www.scopus.com). the first search in the three databases took place in December 2020. A new update for possible inclusion of new studies was carried out in these same databases in April 2022, following the same selection and systematic search criteria. Gray literature was not used and there was no manual search for studies.

Citations were exported as a shared pool to Mendeley's citation manager software. Two independent reviewers (IZA and GMA) assessed whether selected titles and abstracts meet predetermined eligibility criteria. The articles chosen after reading the titles and abstracts were read in full and re-analyzed for eligibility criteria. Any disagreements were settled by an independent third party (PSSC).

Data extraction

Information on data extraction was related to: 1) author, country and year of publication; 2) study design – experimental or clinical trial; 3) population – human, animal, cell cultures and mutation type; 4) intervention – dose, concentration and duration of tratment and/or incubation time; 5) presence of a group and/or experimental control

(another bioactive compound, drug and/or placebo; 6) results – quantitative and qualitative data e 7) main outcome.

Methodological quality assessment

The methodological quality assessment was performed using the checklist for Quasi-Experimental Studies, prepared by the Joana Briggs Institute (TUFANARU et al., 2020) and recommended by Tran et al. (2021). This tool contains nine criteria to be judged: "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 "not applicable", when is not applicable report the information requested in the item. The final score is the number of "yes" scored divided by the maximum score (9) and multiplied by 100. Scores above 70% were considered of high methodological quality (LEWIS et al., 2017) (Tab. 1).

Table 1 – Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies (nonrandomized experimental studies).

Question	**Answer**
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes, No, Unclear or Not Applicable
2. Were the participants included in any similar comparisons?	
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	
4. Was there a control group?	
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	
7. Were the outcomes of participants included in any comparisons measured in the same way?	
8. Were outcomes measured in a reliable way?	
9. Was appropriate statistical analysis used?	

Risk of bias assessment

Two independent reviewers (IZA and PMF) assessed the risk of bias by adapting the tool suggested by the World Cancer Research Fund/University of Bristol for cell line studies [13]. This instrument has six questions, which can be answered between "yes," "no," "not clear," or "not applicable." The risk of bias for each study was considered according to the number of "yes" answered in the sum. of the questions: (a) low risk of bias, if the studies obtained more than 70% of "yes"; (b) moderate risk of bias if the scores

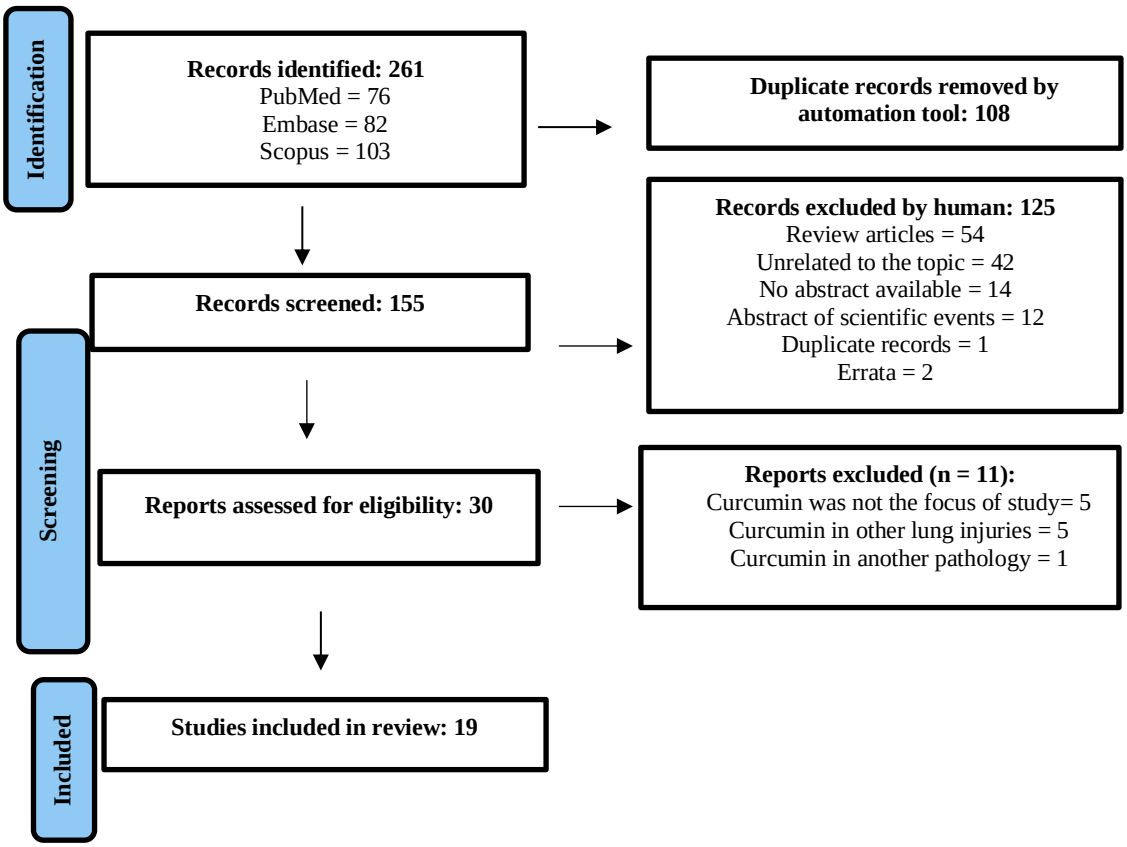
of “yes” were between 50% and 69%, and (c) high risk of bias if “yes” scores were below 49% (MAGRIN et al., 2020). Disagreements between authors were discussed with a third reviewer (PSSC) until a consensus was reached.

RESULTS

Systematic search and selection

In the initial phase, 261 articles were identified from three databases. After removing the duplicates using a reference management tool, 155 articles remained for the first evaluation based on titles and abstracts. Of these, 125 were excluded for not meeting the inclusion criteria. No studies could be added through the gray literature, and no studies were added based on reading the reference list of included studies. In the end, of the 30 articles read in full text, 19 were qualified for the inclusion and extraction of data (Fig. 1).

Figure 1 – PRISMA flow diagram indicating the number of studies identified, screened and excluded as well as the number of eligible studies.



Of 19 selected studies, 18 were in vitro studies, 5 were in vitro and in vivo studies with animal models, and 1 were clinical trials. In in vitro studies, the chinese hamster ovary cells, the baby hamster kidney cells and the fisher rat thyroid epithelial cells was

the most commonly used cell line. The human bronchial epithelial cell line was present in eight studies. Thirteen studies examined the ΔF508 mutation and sixteen studies examined curcumin alone, while two studies examined curcumin encapsulated in nanoparticles or in combination with other coumpounds.

Of 5 animal studies, the concentration of curcumin utilized in three studies was 45 mg/kg/day, one study used 100 mg/kg/day and, another one, 3.75 mg/kg/day of curcumin encapsulated with nanoparticles. In 4 studies, the mices received oral curcumin for three days and one study administered for four days. In 10 studies, both in vitro and in vivo, were not used a control experiment.

The only one clinical trial included participants with the S1251N mutation, at least 6 years old and assessed the combination of curcumin and genistein, and compared it with free Ivacaftor and Ivacaftor with genistein. The treatment duration was 8 weeks for the three trials.

Study characteristics

The main characteristics of the included studies are represented in Tables 2a and 2b.

Table 2a – Characteristics related to study design, population and intervention of included studies.

Author, year, country	Study Design		Population				Intervention		Control
	Experimental	Clinical Trial	Human	Animal	Cell	Mutation	Dose and concentration	Duration of treatment	
BERKERS et al., 2020	No	Yes	At least 6 years old	No	Intestinal organoids rectal biopsy	S1251N	Curcumin (dose: 102,9 a 138,5 mg/kg/day) + genistein (dose: 3,3 a 5,0 mg/kg/day) 3-4 doses. Ivacaftor (dose: 150 mg, twice daily). Genistein (dose: 5,0 a 10,0 mg/kg/day) + Ivacaftor (dose: 150 mg, twice daily).	8 weeks	Placebo
DRAGOMIR et al., 2004	In vitro	No	No	No	Bronchial epitelial cells homozygous (CFBE); Nasal epitelial cells; BHK cells transfected.	ΔF508	Curcumin at 5 µM or 10 µM	Immediate	No
CHAUDHARY et al., 2019	In vitro	No	No	No	Human bronchial epithelial (CFBE41o-); primary human normal (NHBE) and DHBE-CF cells.	Does not specify	Curcumina 10 - 60 µM (10, 20, 40 and 60 µM)	12 h of incubation	DMSO
LIU et al., 2008	In vitro	No	No	No	Fisher Rat thyroid (FRT) epithelial cells.	G551D	Curcumin at 20 µmol/L	60 min of incubation	DMSO and Genistein
GONÇALVES et al., 2017	In vitro	No	No	No	CFBE41o- human bronchial epithelial cells; CFTE29o - human tracheal epithelial;	ΔF508	120 µM, 165 µM and 220 µM of Cur/TBCP2	Incubation for 16h	No

					16HBE14o - normal human bronchial epithelial.				
BERGER et al., 2005	In vitro	No	No	No	Cultures of human airway epithelia were obtained from non-CF and CF bronchus.	ΔF508	Curcumin at 10 µM and 50 µM	Incubation at 27°C for 18h	AMPc agonists and Genistein
YU et al., 2011	In vitro	No	No	No	Chinese hamster ovary cells.	G551D	Curcumin at 5 µM, 10 µm and 30 µM	Immediate	Genistein
DEKKERS et al., 2016	In vitro	No	No	No	Rectal organoids derived from CF subjects	S1251N; G551D; ΔF508	Curcumin at 0 to 200 µM	Incubation for 48h	VX-770 and genistein
EGAN et al., 2004	In vitro	No	No	Mice	Baby hamster kidney cells	ΔF508	Curcumin at 0, 1, 5 and 10 µM Mice given 45 mg of curcumin per kilogram of body weight by mouth	Cells: Incubated at 26°C for 16 hours; Mice: Daily for 3 days.	No
GRUBB et al., 2005	In vitro	No	No	Mice	Baby hamster kidney cells; Human airway epithelial cells	ΔF508	In vitro: Curcumin at 0-50 µM; In vivo: The mice were dosed orally three times per day (45 mg/kg) for 3 days at 8h intervals with curcumin.	Incubation for 3h to 24h	In vivo: Alimentum contained no curcumin
LIPECKA et al., 2006	In vitro	No	No	No	CEPAC-1 (pancreatic duct cellderived from CF patient); CALU-3 (human airway cells derived from serous cells of submucosal glands; HeLa cells.	ΔF508	Curcumin at 25 and 50 µM	The incubation times were as follows: CFPAC-1 cells, 2, 4, and 16 h; ΔF508-CFTR and WT-CFTR HeLa cells, 2 and 4 h; and CALU-3 cells, 16 h.	No

LOO et al., 2004	In vitro	No	No	No	Baby hamster kidney cells	ΔF508	Curcumin at 0, 0.3, 1, 3, 10, 30 µM	Cells incubated for 28h at 37°C or at 27°C in the absence of curcumin and thapsigargin	No
HARADA et al., 2007	In vitro	No	No	Mice	Chinese hamster ovary cells; Baby hamster kidney cells	ΔF508	Curcumina at 0, 10, 20 and 50 µM; In vivo: test animals were giver 100 mg of curcumin per kilogram of body weight, orally, administered daily for 3 days.	Incubation for 24h	No
SONG et al., 2004	In vitro	No	No	Mice	Fisher Rat thyroid (FRT) epithelial cells	ΔF508	In vitro: Curcumin at 40 µM; In vivo: Alimentum or Peptamen with curcumin (45 mg/kg/dia)	Incubation for 24h at 27°C or 37°C	Me_2SO
WANG et al., 2016	In vitro	No	No	No	HEK-293T and FRT cells	W1282X	Curcumin at 30 and 40 µM; VX-770 at 300 nM or 5 µM	Immediate	No
CARTIERA et al., 2010	In vivo	No	No	Mice	Serum and tissue	ΔF508	Each mouse was orally administered (1) free curcumin: total of 3.75 mg, (2) non-drug loaded NPs (blank vehicle control), (3) curcumin NPs at a low-dose: total curcumin encapsulated amount equivalent to 3.75 mg, and (4) curcumin NPs at a highdose: curcumin amount released from nanoparticles at Day 4 equivalent to 3.75 mg.	3 times daily over a three day period	Free curcumin

NOREZ et al., 2006	In vitro	No	No	No	Cell culture of human nasal airway epitelial derived from a CF patient	ΔF508	Curcumin at 10 µM	Incubation for 2h at 37°C	No
WANG et al., 2016	In vitro	No	No	No	HEK-293T and HeLa cells	Δ1198; G551D; W1282X	Curcumin at 30 µM	Immediate	No
BERNARD et al., 2009	In vitro	No	No	No	Human airway epithelial cell; HEK-293T cells	Δ1198; G551D; ΔF508	Curcumin at 0, 0.5, 1, 5, 10, 20, 30 and 50 µm	Incubation for 10 or 15 min at 37°C	No

BHK = baby hamster kidney cells, CFBE = cystic fibrosis human bronchial epitelial cells, NHBE = human normal bronchial epitelial, DHBE – CF = disease bronchial epitelial cells cystic fibrosis, TLR2 = toll-like receptor-2, PGN = peptidoglycan, SP1 protein = transcription fator specificity protein 1, FRT = fisher rat thyroid cells, AMP-c = cyclic adenosine monophosfate, TBCP2 = MeOx6-THF19-MeOx6, WT = wild type cells, FSK = forskolin, VX-770 = Ivacaftor, VX-809 = Lumacaftor, NPD = nasal potential difference, RPD = rectal potential difference, SERCA = sarcoplasmic/endoplasmic reticulum calcium, CEPAC = pancreatic duct cell, CALU = human airway cells derived from serous cells of submucosal glands, K18 = keratin 18, ER = endoplasmatic reticulum, P-gp = P-glycoprotein, CHO = chinese hamster ovary cells, CRT = calreticulin, HEK 293 = human embryonic kidney 293 cells, Po = single channel open probability, Pos = single channel open probabilities, NBD = nucleo binding dimerization, NP = nanoparticles, PLGA = poly-lactic-co-glycolicacid, ATP = adenosine triphosphate.

Table 2b – Objective, results, main outcomes, methodological quality and risk of bias of included studies.

Author, year, country	Objective	Results	Outcomes	Methodological quality	Risk of Bias
BERKERS et al., 2020	To evaluate whether the combinations of curcumin, genistein and ivacaftor would be efficacious in people carrying the S1251N mutation and investigate the plasma levels of theese coumpounds in patients.	Ivacaftor - significant improvement in all clinical outcome parameters tested (ppFEV1; airway resistance; sweat chloride concentration; quality of life; fecal elastase concentration and BMI). Curcumin + genistein - small statistically significant change of SCC and airway resistance.	No clear clinical effect was observed of the treatment with curcumin and/or genistein.	+	NA

DRAGOMIR et al., 2004	To test the effect of curcumin on cultured CF airway epithelial cells and on nasal epithelial cells isolated from CF patients.	Curcumin show a small effect on the net cAMP-mediated (CFTR-mediated) chloride efflux in BHK cells, but no effect on this efflux in an airway epithelial cell line and in native nasal epithelial cells from CF patients.Curcumin not cause a noticeable shift of ΔF508-CFTR to the plasma membrane.	Curcumin has no significant effect on CFTR-mediated chloride efflux in the target cells of a possible treatment of CF patients, the airway epithelial cells.		Moderate
CHAUDHARY et al., 2019	To show that curcumin treatment could dysregulated the expression and function of TLR2 in CF airway epithelial cells by a down-modulated process.	Curcumin suppresses the protein expression of TLR2 in CFBE41o- cells. Curcumin accelerates proteasomal degradation of SP1 protein, resulting in TLR2 down-regulation in CF cells.	Curcumin down-regulates TLR2 gene expression and function in CF bronchial epithelial cells possibly by accelerating SP1 degradation		Moderate
LIU et al., 2008	To demonstrated if curcumin can restore the imapired chloride conductance of G551D mutant CFTR.	20 µmol/L curcumin elevated the AMP-c dependente chloride current by more than 200-fold.	20 µmol/L curcumin can restore the impaired chloride conductance of G551D mutant CFTR.		High
GONÇALVES et al., 2017	To provide evidences that TBCP2 can facilitate de curcumin penetration in normal and CF cells.	The incubation of ΔF508 CFTR cell lines with Cur/TBCP2 induces the relocation of the mutated CFTR protein at the plasma membrane.	Curcumin penetration in normal and ΔF508-CFTR human airway epitelial cell lines is facilitaded by TBCP2		Low
BERGER et al., 2005	To test the hypothesis that curcumin stimulate CFTR chloride channel activity.	Curcumin stimulated Cl channel activity by the presence of ATP and only occurred in channels that had been phosphorylated by PKA	Curcumin increased the activity of both WT and ΔF508 channels and the Cl transport in non CF airway epithelia but not in CF epthelia		Low
YU et al., 2011	To investigate the effect of curcumin, genistein and their combined application on G551D-CFTR activity.	Curcumin increased G551D-CFTR channel currents less than genistein did at their maximally effective concentrations. Curcumin further increased the channel activity of G551D-CFTR that had been already maximally potentiated by genistein, up to ~50% of the WT-CFTR level.	The combined application of genistein and curcumin over a lower concentration range synergistically rescued the gating defect of G551D-CFTR.		Moderate

DEKKERS et al., 2016	To test the impact of potentiator combinations (VX-770, genistein and curcumin) on mutant CFTR function in excised rectal biopsies and in organoids generated from human tissues.	Curcumin, in combination with VX-770 was highly effective at suboptimal dose in organoids with G551D, suggesting that CFTR-G551D is more sensitive to curcumin than CFTR-S1251N; CFTR-ΔF508 homozygous organoids is synergistically repaired by VX-770 and genistein, but not by curcumin.	VX-770, genistein and curcumin in double or triple combinations can synergize in restoring CFTR-dependent fluid secretion in primary CF cells and support the use of multiple potentiators for treatment of CF.		Moderate
EGAN et al., 2004	To test the capacity of curcumin to correct aspects of the CF defect in cell lines and mice expressing ΔF508-CFTR.	After curcumin treatment, the average baseline NPD decreased from –27.9 ± 0.77 mV to –10.8 ± 0.62 mV, approaching the values in wild-type mice; Curcumin treatment resulted in the surface expression of a quantity of ΔF508 CFTR protein that was +25% of that which could be achieved through low-temperature incubation.	Curcumin treatment may be able to correct defects associated with the homozygous expression of ΔF508 CFTR.		High
GRUBB et al., 2005	To investigate the effect of curcumin and thapsigargin in human airway epithelial cells to determine if they could induce ΔF508 CFTR maturation and Cl secretion. In animals cells, to determine if theese compounds coukd interfere with the interaction between calnexin and CFTR and correct the ΔF508 CFTR misfolding defect.	None of the curcumin doses tested significantly reduced the CFTR– calnexin interaction, nor did they result in ΔF508CFTR maturation; None evidence of mature ΔF508 CFTR in any of the curcumin-treated preparations (0, 20, and 40 uM curcumin for 18 h) was found; CF mice exhibit defective apical membrane Cl conductance and Na hyperabsorption and curcumin did not modify these defects	Curcumin failed to induce maturation of ΔF508 CFTR or induce Cl secretion.		Low
LIPECKA et al., 2006	To test if curcumin could restore a functional ΔF508 CFTR to the plasma membrane acting via the K18 network.	Cells treated with curcumin showed a change in the direction of ΔF508-CFTR to the plasma membrane and reorganization of the K18 network. This change occurred with incubation times of 2h, 4h and 16h, and with curcumin concentrations of 25 and 50µM.	Curcumin treatment induced an important change in the K18 network and, in parallel, allowed ΔF508-CFTR to escape from ER and to anchor in the plasma membrane.		Low
LOO et al., 2004	To test whether thapsigargin or curcumin could correct the processing defects in P-gp and CFTR mutants.	Incubation of the cells for 18 h at 27 °C greatly increased the yield of mature CFTR. Increased amounts of mature CFTR were not detected when the cells were expressed in the presence of thapsigargin or curcumin.	Curcumin is not effective in rescuing misprocessed mutants of P-gp and CFTR.		Hight

HARADA et al., 2007	To determine whether calreticulin (CRT) mediates the effect of curcumin on CFTR.	Curcumin down-regulates CRT expression and increases the expression of WT CFTR in vitro and in vivo, but did not affect ΔF508 CFTR expression.	Although curcumin did not augment DF508 CFTR expression, it enhanced the functional competence of DF508 CFTR induced by 26°C incubation.		Low
SONG et al., 2004	To reproduce and extend the pre-clinical data of Egan et al., 2004. to identify the clinical useful of curcumin in correct ΔF508- CFTR gating and cellular misprocessing	No significant increase in iodide influx was found for the pure and neutraceutical curcumin preparations (1–40 μM); No increase in iodide influx was seen for different times of incubation (0-24h) with 40μM curcumin; Curcumin at 45 mg/kg/day did not significantly affect nasal PDs in ΔF508-CFTR mice	Curcumin was unable to produce functional correction of ΔF508-CFTR processing in epithelial cells in culture models and CF mice.		Low
WANG et al., 2016	To confirm that VX-770 and curcumin stimilate the W1282X-CFTR channels	30 μM curcumin alone increased the open probability (Po) of W1282X-CFTR to about 0.2 by increasing both opening rate and mean burst duration. The subsequent addition of 300 nM VX-770 resulted in W1282X-CFTR channels with exceptionally high Po. W1282X-CFTR-mediated currents were further and substantially stimulated by curcumin when this compound was added after a saturating dose of VX-770. Curcumin stabilized those openings and nearly locked open the truncated channel.	The aditive effects of theVX-770 and curcumin on the Po of the truncated W1282X-CFTR channel indicates that they probably bind to different sites and affect channel gating by different mechanisms.		Low
CARTIERA et al., 2010	To synthesize biodegradable curcumin particles that were able to (1) effectively correct defects associated with CF and (2) improve bioavailability of the compound in vivo across species strains	Mice belonging to the 129 background colony demonstrated an average isoproterenol response of 5.0 mV with curcumin nanopartículas treatment, as compared to a mean response of 0.4 mV with free curcumin. In C57/BL6 mice, an average change of 3.7 mV was seen with curcumin NP treatment, as opposed to 0.4 mV with the free compound. Tissue and serum analysis conducted did not reveal the pharmacokinetic distribution of free curcumin or curcumin nanoparticles.	PLGA nanoparticles encapsulating curcumin enhance the capacity of curcumin to partially correct at least a subset of CF symptoms *in vivo*, both in 129 background and C57/BL6 mouse strains.		NA

NOREZ et al., 2006	TO evaluate the effect of several SERCA inhibitors on the human airway epithelial CF cell line	Several SERCA inhibitors (including curcumin) are able to restore the defective trafficking of ΔF508-CFTR after 2 h of treatment by the alteration of interactions between nascent F508del- CFTR protein in the ER and calnexin.	The decreasing and maintaining a low calcium level in ER is required to prevent the interaction between calnexin and ΔF508-CFTR and, thus, to restore the defective trafficking of endogenous ΔF508-CFTR.		Low
WANG et al., 2016	To investigate the mechanism by which curcumin,activates wild type and mutant CFTR channels.	Curcumin opened CFTR channels by a novel mechanism that required neither ATP nor the second nucleotide-binding domain (NBD2) and potently activated CF mutant channels that are defective for the normal ATP-dependent mode of gating (*e.g.* G551D and W1282X), including channels that lack NBD2.	CFTR channels can be induced to open by an alternative mechanism that bypasses this normal requirement for ATP binding and NBD heterodimerization.		Moderate
BERNARD et al., 2009	To show the cross-linking and channel activating effect of curcumin	The cyclic derivatives of curcumin lack the ability to cross-link CFTR polypeptides but retain the ability to persistently activate CFTR channels in excised membrane patches.	This finding clearly separates the property of curcumin to cross-link CFTR polypeptides into SDS resistant dimers from its ability to irreversibly potentiate channel function.		Low

BHK = baby hamster kidney cells, CFBE = cystic fibrosis human bronchial epitelial cells, NHBE = human normal bronchial epitelial, DHBE – CF = disease bronchial epitelial cells cystic fibrosis, TLR2 = toll-like receptor-2, PGN = peptidoglycan, SP1 protein = transcription fator specificity protein 1, FRT = fisher rat thyroid cells, AMP-c = cyclic adenosine monophosfate, TBCP2 = MeOx6-THF19-MeOx6, WT = wild type cells, FSK = forskolin, VX-770 = Ivacaftor, VX-809 = Lumacaftor, NPD = nasal potential difference, RPD = rectal potential difference, SERCA = sarcoplasmic/endoplasmic reticulum calcium, CEPAC = pancreatic duct cell, CALU = human airway cells derived from serous cells of submucosal glands, K18 = keratin 18, ER = endoplasmatic reticulum, P-gp = P-glycoprotein, CHO = chinese hamster ovary cells, CRT = calreticulin, HEK 293 = human embryonic kidney 293 cells, Po = single channel open probability, Pos = single channel open probabilities, NBD = nucleo binding dimerization, NP = nanoparticles, PLGA = poly-lactic-co-glycolicacid, ATP = adenosine triphosphate.

Outcomes

Clinical effect in humans

There was a significant improvement in the clinical parameters of pulmonary function, sweat chloride concentration, quality of life assessment, Body Mass Index and fecal elastase with the use of Ivacaftor in the only one study in individuals with CF (BERKERS et al., 2020). There was a small but significant reduction in sweat chloride concentration and airway resistance using curcumin and genistein. However, plasma curcumin concentration was not detected after treatment, and that of genistein was between 3 and 14 µg/L, both substantially lower than that found with Ivacaftor (1942 and 1160 µg/L).

Intracellular chlorine concentration, conductance, and efflux

The ability of curcumin to restore regular intracellular chloride transport by CFTR: curcumin showed a negligible effect on chlorine efflux only in kidney cells from baby rats transfected with the ΔF508 mutation, causing no significant changes in human CF bronchial epithelial cells and nasal epithelial cells isolated from patients carrying the mutation ΔF508 (DRAGOMIR et al., 2014). Liu et al. (2008) demonstrated that curcumin effectively stimulated chloride conductance in thyroid epithelial cells from fisher rats transfected with the FC G551D mutation.

In human bronchial epithelial cells from CF carriers and non-carriers, curcumin was able to increase the activity of the chlorine channel, i.e., it reduced the closing time and prolonged the opening time of CFTR channels, but it was not efficient in stimulating the transport of epithelial chlorine in the ΔF508 mutant channels (BERGER et al., 2005). In the experiment by Egan et al. (2004), treatment with curcumin resulted in 25% of ΔF508-CFTR protein expression on the cell surface compared to the level achieved by incubation at low temperatures (26°C). The corrective capacity of the chlorine channel by curcumin was also demonstrated by Norez et al. (2006). In this study, the concentration of 620 Nm of curcumin caused a 45% stimulation of iodine efflux in nasal epithelial cells homozygous for the ΔF508 mutation. In contrast to the positive results described, Song et al. (2004) did not demonstrate an increase in iodine influx in ΔF508-CFTR fisher rat

thyroid cells incubated for 24 hours with 40 μM of pure curcumin, not even when this same experiment was maintained at 27ºC.

Ability to activate function, induce maturation and restore CFTR opening defect

The influence of curcumin on CFTR activity: the 10 μM concentration of curcumin stimulated the activity of both wild-type (WT) and ΔF508 CFTR channels ($p < 0.05$), increasing the channel opening time and reducing the closing time ($p < 0.05$), but was not able to stimulate the transport of chloride in the epithelium of the airways of individuals with CF (BERGER et al., 2005).

The use of polymers that facilitate the solubilization of curcumin has been studied (GONÇALVES et al., 2017). The formulation of methyl-2-oxazoline (MeOx) and tetrahydrofuran (THF) (MeOx6-THF19-MeOx6) (TBCP2) copolymer with curcumin, Cur/TBCP2, at a concentration of 400/2000 μg induced the relocation of ΔF508-CFTR to the plasma membrane and promoted the functionality of these chloride channels on the cell surface. In baby hamster kidney cells or human bronchial epithelial cells homozygous for ΔF508,10μM, curcumin failed to show significant movement of CFTR to the plasma membrane, evidencing a cytoplasmic localization of this protein (DRAGOMIR et al., 2014).

Nasal potential difference and rectal potential difference

Correction of the chlorine transport defect by curcumin through nasal potential difference: in the experiment by Egan et al. (2004), mice homozygous for the ΔF508 mutation received 45 mg/kg of body weight daily for three months and had a decrease in mean nasal potential from -27.9 + 0.77 to 10.8 + 0.62 Mv, approaching those of values of wild rats (-8.36 + 0.55 Mv). However, the rectal potential difference analysis performed in this same study to assess intestinal ion transport after curcumin treatment failed to demonstrate a response in the mutant mice.

In contrast to these results, experiments by Song et al. (2004) did not demonstrate correction of nasal potential differences in ΔF508-CFTR homozygous rats that received varying concentrations of curcumin (45 mg/kg/day or 100 mg/kg/day) using different vehicles (Alimentum® and Peptamen®) and administration protocols.

Function repair of CFTR by the growth of organoids

Organoids generated from intestinal tissues through rectal biopsies were used to assess mutant CFTR function. Culture of intestinal organoids from the S1251N mutation exposed to the association of 10 µM of genistein with 50 µM of curcumin showed that the two natural food compounds could induce organoid growth in the presence of 0.128 µM of forskolin (1092%). However, the response was substantially greater when organoids were exposed to VX-770/Ivacaftor alone (3 µM) or associated with genistein (10 µM), 2225%, and 3240%, respectively (WANG et al., 2007).

The repair of CFTR function by analyzing the growth of organoids was the subject of a study by Dekkers et al. (2016). In this trial, curcumin was associated with genistein and VX-770/Ivacaftor and exposed to organoids originating from ΔF508/S1251N, ΔF508/ΔF508, and ΔF508/G551D mutations. It was combining the three compounds synergistically repaired CFTR-dependent epithelial fluid transport in the S1251N mutation. Curcumin in combination with VX-770 was highly effective at suboptimal doses. However, it was not effective in organoids homozygous for ΔF508.

Methodological quality and risk of bias assessment

The methodological quality and the risk of bias assessment for all articles are provided in Chart 1.

Chart 1 – Methodological quality and the risk of bias assessment in individual studies (n=19).

Study	Q1	Q2	Q3	Q4	Q5	Q6	Total (% Score Yes)	Risk of Bias
BERKERS et al., 2020	NA	NA	NA	NA	NA	NA	NA	NA
DRAGOMIR et al., 2004	Y	Y	Y	N	Y	N	66,6	Moderate
CHAUDHARY et al., 2019	Y	Y	N	N	Y	N	50,0	Moderate
HAO et al., 2008	Y	Y	N	N	UC	N	33,3	High
GONÇALVEZ et al., 2017	Y	Y	Y	Y	Y	N	83,3	Low
BERGER et al., 2005	Y	Y	Y	Y	Y	N	83,3	Low
YU et al., 2011	Y	Y	N	N	Y	N	50,0	Moderate
DEKKERS et al., 2016	Y	Y	N	N	Y	Y	66,6	Moderate
EGAN et al., 2004	N	N	Y	N	N	N	16,6	High
GRUBB et al., 2005	Y	Y	Y	Y	Y	N	83,3	Low
LIPECKA et al., 2006	Y	Y	Y	Y	Y	N	83,3	Low
LOO et al., 2004	Y	N	N	N	Y	N	33,3	High
HARADA et al., 2007	Y	Y	Y	Y	Y	N	83,3	Low
SONG et al., 2004	Y	Y	Y	Y	Y	N	83,3	Low
WANG et al., 2016	Y	Y	Y	Y	Y	N	83,3	Low
CARTIERA et al., 2010	NA	NA	NA	NA	NA	NA	NA	NA
NOREZ et al., 2006	Y	Y	Y	Y	Y	N	83,3	Low
WANG et al., 2007	Y	Y	N	N	Y	Y	66,6	Moderate
BERNARD et al., 2009	Y	Y	Y	Y	Y	Y	100	Low

Q1: Have the cells been obtained from a validated repositor that guarantees cell verification or have the cells been appropriately independently verified?; Q2: Have sufficient biological and technical repeats of the experiments been conducted and were appropriate controls included?; Q3: Were different cell lines from the same Cystic Fibrosis Mutation used in the study?; Q4: Are the treatment regime comparable between different cell lines?; Q5: Was selective reporting of results avoided?; Q6: Were cell lines from

different Cystic Fibrosis mutations compared? This implies a significant effect that is relevant more generally to Cystic Fibrosis. Y: yes; N: no; NA: not applicable.

DISCUSSÃO

This systematic review on the effects of curcumin on CF gathered a methodologically rigorous synthesis of evidence, predominantly from in vitro studies, that points to curcumin's additive or synergistic function when associated with other potentiators of CFTR action (such as Ivacaftor). This positive effect seems to be related to genetic mutations that lead to a defect in the opening of the chloride and sodium channel, allowing the repair and stabilization of the functionality of this protein. However, the results are conflicting regarding the effect of this bioactive compound in inducing CFTR maturation, its transport between the ER and the plasma membrane, and the expression of its function on the cell surface. In clinical studies in humans, research is still incipient, especially regarding the determination of formulations that have a more effective pharmacokinetic action and, consequently, promote improvement in the clinical parameters of patients with CF.

The ability of curcumin to produce the functional correction of ΔF508-CFTR in different cell cultures and in CF mice is subject to conflicts between experiments. Egan et al. (2004) were pioneers in vitro and in vivo studies with curcumin in models transfected with ΔF508-CFTR. Their results signaled a possible promising clinical use of this food compound in treating CF. However, this study presented a high risk of bias. Its findings were strongly refuted by experiments with better methodological qualities and low risk of bias, which used mice from the same genetic lines, different cell cultures, and a broader spectrum of protocols, with variations in dose and duration of curcumin treatment (SONG et al., 2004; GRUBB et al., 2006).

The most robust evidence for the action of curcumin on the expression and function of CFTR is related to mutations that lead to defects in the opening and closing of the chlorine channel (WANG et al., 2007; WANG et al., 2016; DEKKER et al., 2016). In these mutations, CFTR proteins are transported to the cell membrane but do not respond to stimulation by cAMP. Therefore, curcumin may have therapeutic value in CF patients carrying mutations that affect the channel's functionality already located on the cell surface (Δ1198-CFTR, G551D-CFTR, and W1282X-CFTR). In combination with other enhancers of CFTR function, Curcumin can not only increase channel opening time but also keep it open longer. In human bronchial epithelial cells with CF, curcumin may

also play its anti-inflammatory properties by attenuating pro-inflammatory receptors, such as the toll-like receptor 2. This mechanism points to a possible role of curcumin in controlling infections associated with airway inflammation in individuals with CF (LIPECKA et al., 2006).

The use of nasal potential difference measurement is helpful to correlate the transport of sodium and chloride across the cell membrane and determine the effectiveness of treatment in patients with CF. Studies that found no induction of chlorine transport by curcumin in the nasal epithelium of ΔF508-CFTR rats used free curcumin and did not add substances that could improve the absorption of this bioactive compound and even protect against degradation of the gastrointestinal tract (SONG et al., 2004; GRUBB et al., 2006).

To infer that a longer exposure time to curcumin could decrease sodium absorption and correct the defect in chlorine conductance, Grubb et al. [9] treated ΔF508-CFTR rats with 45 mg/kg of curcumin for 5 to 7 days. The longer treatment time did not induce chlorine secretion and did not reduce sodium hyperabsorption in the nasal epithelium of mutant rats. Cartiera et al. (2010) demonstrated a statistically significant response in the nasal potential difference in 129 mice homozygous for the ΔF508 mutation that received encapsulated curcumin in nanoparticles compared to the free form.

The reduced stability of curcumin in water, its poor absorption from the intestinal tract, and the rapid hepatic metabolism are limiting factors for using this natural agent in treating individuals with CF. However, the association of substances that help the penetration of curcumin into the CFTR and, therefore, promote the expression and function of the mutant channel may be an advantageous pharmacological strategy (GONÇALVES et al., 2017). The encapsulation of curcumin in nanoparticles is an example of a viable alternative for better therapeutic efficacy. It exhibited higher bioelectric currents in the nasal epithelium of rats heterozygous for ΔF508 (CARTIERA et al., 2010).

In CF mutations associated with a defect in the opening of chloride channels, such as G551D-CFTR, curcumin was able to increase the activity of the channel that was already maximally potentiated by the compound genistein in Chinese hamster ovary cells. Curcumin concentrations of 5, 10, and 30 μM added to 10, 20, 40, and 80 μM of genistein showed a synergistic effect in restoring the channel opening defect to up to 50% of the wild-type CFTR level (YU et al., 2011).

In thyroid cells from fisher rats expressing the W1282X-CFTR mutation, exposure to 30 µM of curcumin followed by the addition of 300 nM of VX-770 (saturated dose) was efficient in stimulating the maximal opening capacity of the mutant chlorine channel (Po > 0.9). This same concentration of curcumin provoked stimulation of the low-opening mutant CFTR channels (W1282X and G551D) through a mechanism independent of ATP binding and dimerization of the two nucleotide-binding domains, but that requires phosphorylation of the R domain by protein kinase A (WANG et al., 2016).

The evaluated studies that had their methodological qualities compromised did not have a similar treatment regimen beyond the exposure of interest, did not have a control group, or did not perform the exact measurements before and after exposure. Regarding the risk of bias, studies scored at high risk showed a more frequent tendency to lack comparison of different CF gene mutations for the same cell lineage. We identified that the two evaluations were consistent, as they recognized the same limitations across the studies.

REFERÊNCIAS

BERGER, A. L.; RANDAK, C. O.; OSTEDGAARD, L. S.; KARP, P. H.; VERMEER, D. W. et al. Curcumin stimulates cystic fibrosis transmembrane conductance regulator Cl- channel activity. **The Journal of Biological Chemistry**, Baltimore, v. 280, n. 7, p. 5221-5226, 2005. https://doi: 10.1074/jbc.M412972200.

BERKERS, G.; VAN DER MEER, R.; VAN MOURIK, P.; VONK, A. M.; KRUISSELBRINK, E. et al. Clinical effects of the three CFTR potentiator treatments curcumin, genistein and ivacaftor in patients with the CFTR-S1251N gating mutation. **Journal of Cystic Fibrosis**, Amsterdam, v. 19, n. 6, p. 955-961, 2020. https://doi: 10.1016/j.jcf.2020.04.014.

BERNARD, K. et al. Curcumin cross-links cystic fibrosis transmembrane conductance regulator (CFTR) polypeptides and potentiates CFTR channel activity by distinct mechanisms. **The Journal of Biological Chemistry**, v. 284, n. 45, p. 360754-65, 2009. https://doi: 10.1074/jbc.M109.056010.

CARTIERA, M. S.; FERREIRA, E. C.; CAPUTO, C.; EGAN, M. E.; CAPLAN, M. J.; SALTZMAN, W. M. et al. Partial correction of cystic fibrosis defects with PLGA nanoparticles encapsulating curcumin. **Molecular Pharmaceutics**, Washington, v. 7, n. 1, p. 86-93, 2010. https://doi: 10.1021/mp900138a.

CHAUDHARY, N. et al. Curcumin Down-Regulates Toll-Like Receptor-2 Gene Expression and Function in Human Cystic Fibrosis Bronchial Epithelial Cells. **Biological & Pharmaceutical Bulletin**, v. 42, n. 3, p. 489-495, 2019. https://doi: 10.1248/bpb.b18-00928.

CUTTING, G. R. Cystic fibrosis genetics: from molecular understanding to clinical application. **Nature Reviews Genetics**, Londres, v. 16, n. 1, p. 45-56, 2015.
DEKKERS, J. F. et al. Potentiator synergy in rectal organoids carrying S1251N, G551D, or F508del CFTR mutations. **Journal of Cystic Fibrosis**, v. 15, n. 5, p. 568-578, 2016. https://doi: 10.1016/j.jcf.2016.04.007.

DRAGOMIR, A. Curcumin does not stimulate cAMP-mediated chloride transport in cystic fibrosis airway epithelial cells. **Biochemical and Biophysical Research Communications**, v. 322, n. 2, p. 447-451, 2014. https://doi: 10.1016/j.bbrc.2004.07.146.

EGAN, M. E.; PEARSON, M.; WEINER, S. A.; RAJENDRAN, V.; RUBIN, D. et al. Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. **Science**, Nova Iorque, v. 304, n. 5670, p. 600-602, 2004. https:// doi: 10.1126/science.1093941.

FARRELL, P. M.; ROCK, M. J.; BAKER, M. W. The Impact of the CFTR Gene Discovery on Cystic Fibrosis Diagnosis, Counseling, and Preventive Therapy. **Genes**, v. 11, n. 4, p. 401, 2020. https://doi: 10.3390/genes11040401.

GONÇALVES, C. et al. Curcumin/poly(2-methyl-2-oxazoline-b-tetrahydrofuran-b-2-methyl-2-oxazoline) formulation: An improved penetration and biological effect of curcumin in F508del-CFTR cell lines. **European Journal of Pharmaceutics and Biopharmaceutics**, v. 117, p. 168-181, 2017. https://doi: 10.1016/j.ejpb.2017.04.015.

GRUBB, B. R. et al. SERCA pump inhibitors do not correct biosynthetic arrest of deltaF508 CFTR in cystic fibrosis. **American Journal of Respiratory Cell and Molecular Biology**, v. 34, n. 3, p. 355-363, 2006.

HARADA, K. et al. Curcumin enhances cystic fibrosis transmembrane regulator expression by down-regulating calreticulin. **Biochemical and Biophysical Research Communications**, v. 353, n. 2, p. 351-356, 2007. https://doi: 10.1016/j.bbrc.2006.12.036.

LEWIS, S. J.; GARDNER, M.; HIGGINS, J.; HOLLY, J. M. P.; GAUNT, T. R et al. Developing the WCRF International/University of Bristol Methodology for Identifying and Carrying Out Systematic Reviews of Mechanisms of Exposure-Cancer Associations. **Cancer Epidemiology, Biomarkers & Prevention**, Philadelphia, v. 26, n. 11, p. 1667-1675, 2017. https://doi: 10.1158/1055-9965.EPI-17-0232.

LIPECKA, J. et al. Rescue of DeltaF508-CFTR (cystic fibrosis transmembrane conductance regulator) by curcumin: involvement of the keratin 18 network. **The Journal of Pharmacology and Experimental Therapeutics**, v. 317, n. 2, p. 500-505, 2006. https://doi: 10.1124/jpet.105.097667.

LIU, X. et al. Natural Compound Curcumin-a Channel Potentiator Rather Than a Corrector of the Defective Intracellular Processing of ΔF508 Mutant Cystic Fibrosis Transmembrane Conductance Regulator. **Chemical Research in Chinese Universities**, v. 24, n. 2, p. 200-203, 2008. https:// 10.1016/S1005-9040(08)60041-0.

LOO, T. W.; BARTLETT, M. C.; CLARKE, D. M. Thapsigargin or curcumin does not promote the maturation of processing mutants of the ABC transporters, CFTR, and P-glycoprotein. **Biochemical and Biophysical Research Communications**, v. 325, n. 2, p. 580-585, 2004. https://doi: 10.1016/j.bbrc.2004.10.070.

MAGRIN, G. L.; STRAUSS, F. J.; BENFATTI, C. A. M.; MAIA, L. C.; GRUBER, R. Effects of Short-Chain Fatty Acids on Human Oral Epithelial Cells and the Potential Impact on Periodontal Disease: A Systematic Review of In Vitro Studies. **International Journal of Molecular Sciences**, Basel, v. 21, n. 14, p. 1-19, 2020. https://doi: 10.3390/ijms21144895.

NOREZ, C. et al. Maintaining low Ca2+ level in the endoplasmic reticulum restores abnormal endogenous F508del-CFTR trafficking in airway epithelial cells. **Traffic**, v. 7, n. 5, p. 562-573, 2006. https://doi: 10.1111/j.1600-0854.2006.00409.x.
PAGE, M. J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. **BMJ Medicine**, v. 372, n. 71, 2021. https://doi: 10.1136/bmj.n71.

REN, C. L. et al. Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis. **Annals of the American Thoracic Society**, v. 15, n. 3, p. 271-280, 2018. https://doi: 10.1513/AnnalsATS.201707-539OT.

SCOTET, V.; L´HOSTIS, C.; FÉREC, C. The Changing Epidemiology of Cystic Fibrosis: Incidence, Survival and Impact of the *CFTR* Gene Discovery. **Genes**, v. 11, n. 6, p. 589, 2020. https://doi: 10.3390/genes11060589.

SONG, Y. et al. Evidence against the rescue of defective DeltaF508-CFTR cellular processing by curcumin in cell culture and mouse models. **Journal of Biological and Chemical Sciences**, v. 279, n. 39, p. 40629-40633, 2004. https://doi: 10.1074/jbc.M407308200.

TRAN, L.; TAM, D. N. H.; ELSHAFAY, A.; DANG, T.; HIRAYAMA, K et al. Quality assessment tools used in systematic reviews of in vitro studies: a systematic review. **BMC Medical Research Methodology**, Londres, v. 21, n. 1, p. 1-13, 2021. https://doi.org/10.1186/s12874-021-01295-w.

TUFANARU, C.; MUNN, Z.; AROMATARIS, E.; CAMPBELL, J.; HOPP, L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). **Joanna Briggs Institute Reviewer's Manual**. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/.

WANG, W. et al. Curcumin opens cystic fibrosis transmembrane conductance regulator channels by a novel mechanism that requires neither ATP binding nor dimerization of the nucleotide-binding domains. **The Journal of Biological Chemistry**, v. 282, n. 7, p. 4533-4544, 2007. https://doi: 10.1074/jbc.M609942200.

WANG, W. et al. Robust Stimulation of W1282X-CFTR Channel Activity by a Combination of Allosteric Modulators. **Plos One**, v. 11, n. 3, e0152232, 2016. https://doi: 10.1371/journal.pone.0152232.

YU, Y. C. et al. Curcumin and genistein additively potentiate G551D-CFTR. **Journal of Cystic Fibrosis**, v. 10, n. 4, p. 243-252, 2011. https://doi: 10.1016/j.jcf.2011.03.001.

ZEITLIN, P. Can curcumin cure cystic fibrosis? **New England Journal of Medicine**, Boston, v. 351, n. 6, p. 606-608, 2004. https://doi: 10.1056/NEJMcibr041584.