

## The effect of Complementary and Alternative Medicines on the symptoms of Cystic Fibrosis patients: A Systematic Review

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### Abstract

**Background:** Cystic fibrosis (CF) is the most common life-threatening hereditary disease among Caucasian populations. Due to the side effects caused by this disease and the high amount of drugs used by the affected patients, performing extensive research seems necessary to find the treatments with greater effectiveness and fewer side effects. The use of Complementary and Alternative Medicine (CAM) is common in both developing and developed countries, but currently available studies performed on the effectiveness of CAM on improving symptoms and reducing complications of CF patients are very limited.

**Objective:** This systematic review was performed to evaluate the effects of CAM therapies on patients with CF.

**Methods:** Six credible medical databases (including Cochrane, Science Direct, Embase, ISI, PubMed, and Scopus) were investigated from the beginning of 2000 to the end of 2020, in order to find relevant English-language publications.

**Results:** From among 1213 articles screened, 57 studies with 2525 patients were included in this study. These articles were then sub-grouped into four categories, including 'acupuncture', 'body techniques', 'dietary supplements/nutrition/diet', and 'herbal medicine'.

The articles evaluating one of the four parameters of quality of life, pain, pulmonary function, or body mass index were included to be evaluated.

**Conclusion:** Although we have not evaluated all the studies in the field of the effect of complementary medicine on CF, the review consisting of a large number of these articles showed that despite the great potential of complementary and alternative medicines in this field, extensive research is still needed in this regard.

**Key Words:** Complementary and Alternative Medicine, Cystic Fibrosis, Systematic Review.

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## 1- INTRODUCTION

Cystic Fibrosis (CF) is an autosomal hereditary disease caused by some mutations in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene, which is known as a cAMP-regulated chloride channel expressed in several epithelia (1).

The incidence of CF is reported as 1 in 3500 newborns among Caucasian ethnicity (2). As well, it is considered as a common disease with 80,000 cases worldwide, 30,000 of which are living in the USA (3).

Multiple organ systems, including sinopulmonary, gastrointestinal, endocrine, and genitourinary are affected by CF (4). Respiratory symptoms are also observed in over 90% of CF patients. Correspondingly, these manifestations include pertussis-like cough, repeated episodes of bronchiolitis or obstructive bronchitis, recurrent bronchopneumonia, and pulmonary atelectasis (4). Additionally, Sinus disease is very prevalent in CF, involving chronic sinusitis with an increased prevalence rate of nasal polyps (3).

In this regard, other clinical manifestations of this disease are exocrine pancreatic insufficiency, meconium ileus, episodes of bowel obstruction due to the thickened mucus, intussusception, and intestinal volvulus. Furthermore, cholestasis, liver steatosis, focal biliary cirrhosis, multilobular biliary cirrhosis, portal hypertension, and Cholelithiasis can also be seen in the affected patients (5).

The diagnosis of CF is performed based on the results of two positive sweat tests (dosage of chloride in sweat exceeding 60 mEq/L) or molecular genetic analysis of positive CFTR mutations (2 mutations). Additionally, a high level of immunoreactive serum trypsinogen (IRT) is considered in confirming the diagnosis of CF (4, 5).

Despite some decades of research, there is no definitive treatment for CF yet (6). In general, the effective drugs on controlling CF are the followings: adrenergic receptor agonists, NSAIDs, antibiotics, inhaled corticosteroids, leukotriene inhibitors, inhaled anticholinergics, Dornase alpha, and Ivacaftor (7).

Although CF has a low incidence, it has some potentially significant economic effects on health care resources and other social costs, as well as a significant effect on patients' health-related quality of life (HRQOL) (8). The average annual cost listed for this disease was estimated to be about €44,585 per CF patient in 2017 (9)

Due to the lack of definite treatments proposed for CF, the chronic nature of the disease, high treatment costs, and low quality of life, the essence of complementary and alternative medicines (CAM) becomes more apparent.

CAM was previously defined by the National Centre for Complementary and Alternative Medicine as "health care approaches developed outside of mainstream Western, or conventional medicine used for specific conditions or overall well-being" (10).

Some studies have also shown that the prevalence rate of the CAM use in children with CF is ranged from about 45% to 75% (11-13).

To the best of our knowledge, never before has there any systematic review been conducted about the effect of CAM on CF. As a result, this study aimed to assess the clinical trials investigating the effects of CAM on CF.

## 2- MATERIALS AND METHODS

The present study was conducted in terms of the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) guidelines for systematic reviews incorporating a network meta-analysis (14).

The current study was a systematic review of clinical trials conducted on the effects of CAM on CF.

Along with the keyword of “cystic fibrosis”, the literature search included the following keywords for “complementary and alternative medicine”: complementary medicine, alternative medicine, complementary and alternative medicines, herb, plant, extract, diet, dietary supplements, vitamins, acupuncture, relaxation, Mind-body, homeopathy, Ayurveda, traditional Chinese medicine, music, chiropractic, massage, art therapy, aromatherapy, yoga, tai-chi, Religious, and spiritual. Finally, those keywords related to clinical trials were the following: randomized controlled trials (RCTs), randomized clinical trials, randomized clinical trial allocating, single-blind method, cross-over studies, and double-blind method. These investigations were performed in databases of Cochrane, science direct, Embase, ISI, PubMed, and Scopus. To fulfill our purpose, we included English studies published from the beginning of 2000 to the end of 2020. First, two reviewers independently assessed all the studies which met inclusion criteria for the review, during which the title and the abstracts of articles were screened. In the second stage, those studies that seemed relevant were extracted and evaluated in full text. Any disagreement was judged by the third reviewer.

### **2-1. Inclusion criteria**

At this stage, we included all the clinical trials RCTs, uncontrolled trials, and pilot studies that evaluated the effect of any kind of CAM therapies on CF. Thereafter, we set four main parameter measurements as the criteria used for choosing the articles, including quality of life, pulmonary function, body mass index, and pain. These parameters were mentioned more prominently in these studies. Another inclusion criterion was the

articles’ being published in English language from beginning of 2000 to the end of 2020 with no limitation in participants’ age or country.

### **2-2. Exclusion criteria**

After reviewing the full text of the included articles, those that did not measure at least one of the above-mentioned four parameters were excluded.

Considering the methodology of the studies, non-clinical trials, including reviews, cross sectional studies, cohort studies, case series, case reports, animal studies, and in-vitro studies, were excluded.

In regard to the type of the articles, editorial letters, conference papers, posters, and all the publications before 2000 were excluded as well.

### **2-3. Bias assessment**

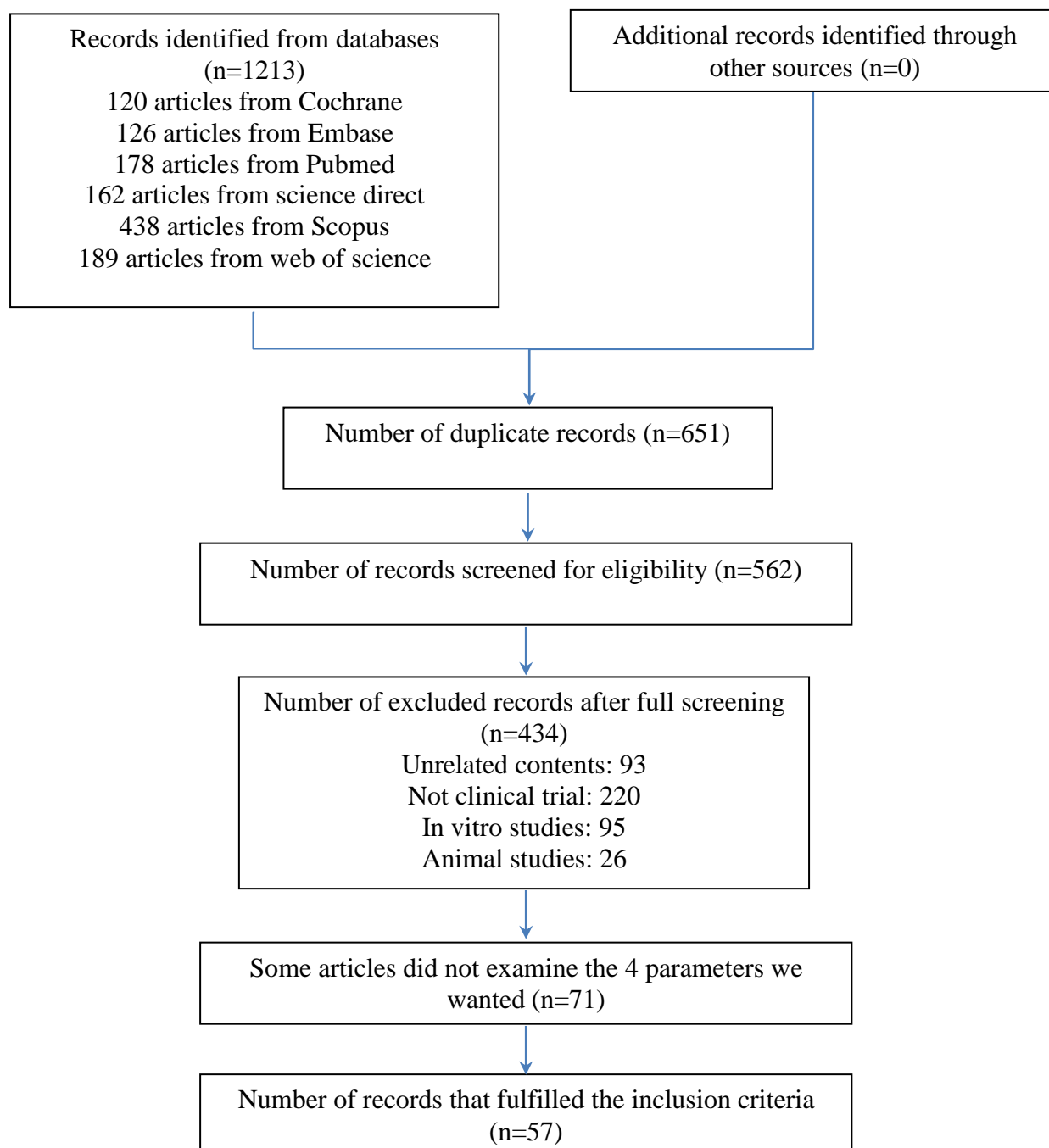
The Cochrane Collaboration tool was then used for assessing the risk of bias (14). In addition, the full text of the reviewed articles and their protocols, if available, were assessed for finding the appropriateness of their content. Afterward, all the main texts were reviewed and then assessed by an epidemiologist collaboration. According to the Cochrane risk of bias tool, items of random sequence generation, allocation concealment, blinding the participants and personnel, blinding outcome’s assessment, incomplete outcome data, selective reporting, and other sources of bias were assessed.

## **3- RESULTS**

In the initial phase of search, 1213 articles were found, of which 562 articles remained after removing the duplicates from the title. Subsequently, 434 articles were removed after reviewing the abstracts of the included articles (due to the following reasons: 93 articles had unrelated contents, 220 of them were not

clinical trials, 95 studies were In vitro studies, and 26 articles were Animal studies). Finally, 128 articles were selected, of which after reviewing the full text of the studies, 71 did not pass our conditions to be included in the

examination of 'the four parameters', so they were deleted subsequently. By applying all these criteria, 57 articles remained for the main analysis. The detailed flow diagram of the study is shown in **Fig. 1**.



**Fig. 1:** Study flowchart

The characteristics of these 57 studies and the bias assessment results are summarized in **Table 1, 2, and 3**. The interventions were divided into four groups, including 1 article in ‘acupuncture’, 10 articles in ‘body techniques’, 45 articles in ‘dietary supplements/nutrition/diet’, and 1 article in ‘herbal medicine’.

The use of body techniques, including Osteopathic manipulative treatment (OMT), summer camp (SC), tai chi (TAI), exercise, massage, yoga, and physiotherapy and massage (PHAM), was also investigated.

It is noteworthy that those articles on dietary supplements/Nutrition/diet evaluated b-carotene, lipid matrix, micronutrients, probiotics, whey protein, growth hormone, magnesium, omega-3,

vitamin D, docosahexaenoic acid, Liprotamase, choline, bisphosphonates, Melatonin, antioxidant, creatine supplementation, Megestrol Acetate, protein-energy supplements, N-acetylcysteine, and zinc.

In this phase, 39 articles (68.42%) were found to be randomized and 18 (31.57%) were non-randomized. Moreover, 27 articles (47.36%) had a placebo group and 30 (52.63%) of them had no placebo group. The reviewed studies were conducted in Australia, Austria, Belgium, Brazil, Canada, Denmark, England, Germany, India, Iran, Israel, Italy, Netherlands, Spain, Sweden, Switzerland, Turkey, The United Kingdom (UK), and The United States of America (USA).

**Table-1:** Timely dispersion of the reviewed articles

Year of study	Article	percent
2000 -2005	13	22.8
2005-2010	14	24.56
2010-2015	12	21.05
2015-2020	18	31.57
Total	57	100

#### 4- DISCUSSION

This systematic review highlights the fact that despite the high necessity and high capacity, just a few studies have been performed on the effect of CAM on CF, and as a result, there is insufficient clinical evidence for a perfect assessment. The use of traditional medicine has been indicated to have some positive effects on various aspects of CF patients. Nevertheless, due to the large number of investigated parameters and their dispersion, we only evaluated 4 items in this study.

We found one article in acupuncture, 10 articles in Body techniques, 46 articles in Dietary supplements/Nutrition/diet, and one article in Herbal medicine (garlic). *Allium sativum* (garlic) has been found to

have immunomodulatory, antimicrobial, antiviral, and anti-inflammatory properties. Additionally, it has the ability of reducing the expression of proinflammatory cytokines (72).

Smyth et al. (2010) in their pilot study, evaluated the effect of garlic on CF patients. In this study, the mean ( $\pm$ SD) of increase in weight, change from baseline FEV1, and modification in clinical score were greater with garlic compared to those of placebo; however, they were non-significant (24). This can be due to the limited sample size of the study, so it is recommended to be reviewed in more extensive clinical trials.

**Table-2:** Definitive data of the reviewed articles

ID	Study (First author, year, country)	Treatment	Categories	Method	Sample Size (total)	Number of subjects in intervention/placebo/ control group	Duration	BMI <sub>1</sub>	QOL <sub>2</sub>	Pain	PF <sub>3</sub>
1	David A. Swender, 2007, USA (15)	OMT	Body techniques	RCT <sup>4</sup> ,SB <sup>5</sup>	33	17/16/0	4 to 7 days	ND <sup>6</sup>	ND	N <sup>7</sup>	N
2	Hannah Blau, 2001, Israel (16)	SC	Body techniques	clinical trial	13	13/0/0	4 weeks	ND	ND	ND	N
3	Siobhán B. Carr, 2018, UK (17)	TAI	Body techniques	RCT	40	40/0/0	9 months	N	N	ND	N
4	Sumita Gupta, 2019, India (18)	exercise	Body techniques	RCT	52	25/0/27	12 months	N	Y <sup>8</sup>	ND	N
5	Dominique Hubert, 2014, USA (19)	OMT	Body techniques	RCT	32	16/8/8	6 months	ND	N	N	ND
6	Kathleen (Kate) Zink, 2019, USA (20)	massage	Body techniques	pilot study	24	12/0/12	10 to 12 weeks	ND	N	N	N
7	Yuan-Chi Lin, 2005, USA (21)	ACU <sup>9</sup>	Acupuncture	pilot study	30	30/0/0	ND	ND	ND	Y	ND
8	Jennifer Ruddy, 2015, USA (22)	YOGA	Body techniques	pilot study	11	11/0/0	8 weeks	N	Y	N	N
9	H.C.Selvadurai, 2001, Australia (23)	exercise	Body techniques	RCT	66	44/0/22	1 week	Y	Y	ND	Y
10	Alan R. Smyth, 2009, UK (24)	Garlic	Herbal medicine	RCT	26	13/13/0	8 weeks	ND	ND	ND	N
11	Christopher McNamara, 2016, USA (25)	YOGA	Body techniques	pilot study	20	20/0/0	10 weeks	ND	N	Y	ND
12	Annemarie Lee, 2008, Australia (26)	PHAM	Body techniques	clinical trial	105	105/0/0	a single session	ND	ND	Y	ND
13	N C <sub>3</sub> obanogÆ lu, 2002, Turkey (27)	b-carotene	Dietary supplements/ Nutrition/diet	pilot study	48	33/0/15	6 months	N	ND	ND	Y
14	Petra Rust, 2000, Austria (28)	b-carotene	Dietary supplements/ Nutrition/diet	RCT	38	13/11/14	24 week	ND	Y	ND	Y
15	S Renner, 2000, Austria (29)	b-carotene	Dietary supplements/ Nutrition/diet	RCT	24	13/11/0	6 months	N	ND	ND	N

ID	Study (First author, year, country)	Treatment	Categories	Method	Sample Size (total)	Number of subjects in intervention/placebo/ control group	Duration	BMI <sub>1</sub>	QOL <sub>2</sub>	Pain	PF <sub>3</sub>
16	Veronique Groleau, 2014, USA (30)	LXS <sup>10</sup>	Dietary supplements/ Nutrition/diet	RCT	63	27/36/0	12 months	N	ND	ND	N
17	Johanna H. Oudshoorn, 2006, Netherlands (31)	micronutrients	Dietary supplements/ Nutrition/diet	RCT	22	11/11/0	3 months	N	ND	ND	N
18	Batia Weiss, 2009, Israel (32)	Probiotic	Dietary supplements/ Nutrition/diet	prospective pilot study	10	10/0/0	6 months	N	ND	ND	N
19	L.C. Lands, 2009, Canada (33)	Pressurized Whey	Dietary supplements/ Nutrition/diet	pilot open- label study	24	24/0/0	1 month	Y	N	N	Y
20	DANA S. HARDIN, 2004, USA (34)	GH <sup>11</sup>	Dietary supplements/ Nutrition/diet	RCT	18	9/0/9	2 year	Y	N	N	Y
21	Clésio Gontijo-Amaral, 2012, USA (35)	magnesium	Dietary supplements/ Nutrition/diet	RCT, DB <sup>12</sup> , CO <sup>13</sup>	44	22/22/0	8 week	N	ND	ND	ND
22	L. Hanssens, 2016, Belgium (36)	omega-3	Dietary supplements/ Nutrition/diet	RCT, DB	15	7/8/0	12 months	N	ND	ND	N
23	Vijaylaxmi Grey, 2003, Canada (37)	whey protein	Dietary supplements/ Nutrition/diet	RCT	21	10/11/0	3 months	N	ND	ND	N
24	Marianne Skov, 2014, Denmark (38)	NAC <sup>14</sup>	Dietary supplements/ Nutrition/diet	RCT	21	11/0/10	4 weeks	ND	ND	ND	N
25	Nemat Bilan, 2019, Iran (39)	synbiotic supplementatio n	Dietary supplements/ Nutrition/diet	RCT	40	18/18/0	6 months	N	ND	ND	N

ID	Study (First author, year, country)	Treatment	Categories	Method	Sample Size (total)	Number of subjects in intervention/placebo/ control group	Duration	BMI <sub>1</sub>	QOL <sub>2</sub>	Pain	PF <sub>3</sub>
26	Stephanie Van Biervliet, 2018, Belgium (40)	Probiotics	Dietary supplements/ Nutrition/diet	RCT, DB, CO	31	17/14/0	4 months	N	ND	N	N
27	A. De Alessandri, 2011, Italy (41)	whey proteins	Dietary supplements/ Nutrition/diet	prospective, open, clinical study	59	59/0/0	36 months	ND	ND	ND	N
28	Yasmeen Abu-Fraiha, 2018, Israel (42)	Vit D	Dietary supplements/ Nutrition/diet	clinical trial	90	90/0/0	2 years	ND	ND	ND	N
29	G. Alicandro, 2012, Italy (43)	DHA <sup>15</sup>	Dietary supplements/ Nutrition/diet	RCT	41	21/20/0	12 month	N	ND	ND	N
30	Drucy Borowitz, 2011, Israel (44)	Liprotamase	Dietary supplements/ Nutrition/diet	phase III 12-month open-label trial	214	214/0/0	12 months	N	ND	ND	N
31	Wolfgang Bernhard, 2019, Germany (45)	Choline	Dietary supplements/ Nutrition/diet	pilot study	10	10/0/0	84 days	ND	ND	ND	Y
32	S. P. Conway, 2004, UK (46)	bisphosphonates	Dietary supplements/ Nutrition/diet	pilot study	59	35/0/24	ND	N	ND	ND	N
33	Claudia de Castro-Silva, 2009, Brazil (47)	Melatonin	Dietary supplements/ Nutrition/diet	RCT	19	9/10/0	21 days	ND	ND	ND	N
34	Maiara Brusco de Freitas, 2017, Brazil (48)	synbiotic supplementation	Dietary supplements/ Nutrition/diet	RCT	58	22/19/17	90 days	Y	ND	ND	N
35	Basilio De Vizia, 2002, Italy (49)	omega 3 fatty acids	Dietary supplements/	prospective study	50	30/0/20	8 month	Y	ND	ND	Y



ID	Study (First author, year, country)	Treatment	Categories	Method	Sample Size (total)	Number of subjects in intervention/placebo/ control group	Duration	BMI <sub>1</sub>	QOL <sub>2</sub>	Pain	PF <sub>3</sub>
			Nutrition/diet								
36	Lisa G Wood, 2001, Australia (50)	Antioxidant	Dietary supplements/ Nutrition/diet	RCT	46	22/24/0	8 weeks	N	ND	ND	N
37	Scott D. Sagel, 2010, USA (51)	Antioxidant	Dietary supplements/ Nutrition/diet	pilot study	17	17/0/0	12 weeks	N	ND	ND	Y
38	Christian P. Braegger, 2003, Switzerland (52)	creatine supplementation	Dietary supplements/ Nutrition/diet	pilot study	18	18/0/0	12 weeks	ND	ND	ND	N
39	Jacqueline A. Jumpsen, 2006, Canada (53)	DHA	Dietary supplements/ Nutrition/diet	clinical trial	4	4/0/0	6 weeks	ND	ND	ND	N
40	Seyed-Ali Jafari, 2013, Iran (54)	Probiotics	Dietary supplements/ Nutrition/diet	RCT	37	20/17/0	1 month	ND	Y	ND	ND
41	Mansi Kanhere, 2017, USA (55)	Vit D	Dietary supplements/ Nutrition/diet	RCT	38	10/10/18	12 weeks	N	ND	ND	N
42	Christina Keen, 2009, Germany (56)	Fatty Acids	Dietary supplements/ Nutrition/diet	RCT,DB	35	30/15/0	3 months	N	ND	ND	N
43	Amanda Leonard, 2009, USA (57)	standardized nutrition	Dietary supplements/ Nutrition/diet	prospective , observational study	247	247/0/0	15-month	Y	ND	ND	ND
44	John D. Lloyd-Still, 2005, USA (58)	DHA	Dietary supplements/ Nutrition/diet	RCT	19	9/10/0	6 months	ND	ND	ND	N

ID	Study (First author, year, country)	Treatment	Categories	Method	Sample Size (total)	Number of subjects in intervention/placebo/ control group	Duration	BMI <sub>1</sub>	QOL <sub>2</sub>	Pain	PF <sub>3</sub>
45	Valerie Marchand, 2000, USA (59)	Megestrol Acetate	Dietary supplements/ Nutrition/diet	RCT	12	6/6/0	12 weeks,	ND	ND	ND	N
46	Vin Tangpricha, 2018, USA (60)	Vit D	Dietary supplements/ Nutrition/diet	RCT,DB	91	46/45/0	3 months	ND	ND	ND	N
47	Gabriel Oliveira, 2009, Spain (61)	Fatty Acid Supplementati on	Dietary supplements/ Nutrition/diet	clinical trial	17	17/0/0	12 months	Y	N	ND	Y
48	Vanessa J Poustie, 2006, London (62)	protein energy supplements	Dietary supplements/ Nutrition/diet	RCT	102	50/0/52	12 months	N	ND	ND	N
49	Pedram Ataee, 2014, Iran (63)	Zinc	Dietary supplements/ Nutrition/diet	clinical trial	30	30/0/0	6 months	Y	ND	ND	Y
50	Ruth E. Grossmann, 2012, USA (64)	Vit D	Dietary supplements/ Nutrition/diet	RCT,DB	30	15/15/0	12 weeks	N	ND	ND	N
51	T Pincikova, 2016, Sweden (65)	Vit D	Dietary supplements/ Nutrition/diet	RCT	16	9/0/4	3 months	ND	Y	ND	Y
52	Scott D. Sagel, 2018, USA (66)	Antioxidant- enriched multivitamin	Dietary supplements/ Nutrition/diet	RCT,DB	73	36/0/37	16 weeks	N	ND	ND	N
53	Joan I. Schall, 2015, USA (67)	LXS	Dietary supplements/ Nutrition/diet	RCT,DB	110	54/56/0	12 months	Y	ND	ND	Y
54	Gratiana Steinkamp, 2000, Germany (68)	oral energy supplement rich in linoleic acid	Dietary supplements/ Nutrition/diet	RCT	36	16/0/20	3 months	ND	ND	ND	N

ID	Study (First author, year, country)	Treatment	Categories	Method	Sample Size (total)	Number of subjects in intervention/placebo/ control group	Duration	BMI 1	QOL 2	Pain	PF 3
55	Matthew A. Tucker, 2019, USA (69)	single antioxidant cocktail	Dietary supplements/ Nutrition/diet	RCT,DB	18	9/9/0	once	N	ND	ND	Y
56	S. Van Biervliet, 2007, Belgium (70)	DHA	Dietary supplements/ Nutrition/diet	RCT,DB	17	9/8/0	12 months	ND	ND	ND	N
57	Ganesh Sharma DNB, 2016, India (71)	Zinc	Dietary supplements/ Nutrition/diet	RCT,DB	40	20/20/0	12 months	N	ND	ND	N

1) Body mass index

3) Pulmonary function

5) Single-blind

7) No (without significant effect)

9) Acupuncture

11) Growth hormone

13) Crossover

15) docosahexaenoic acid

2) Quality of life

4) Randomized clinical trial

6) Not determined

8) Yes (with significant effect)

10) The organized lipid matrix LYM-X-SORB™

12) double-blind

14) N-acetyl cysteine

**Table-3:** Risk of bias for the reviewed articles

ID	Study (First author, year, country)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
1	David A. Swender, 2007, USA	Low	Low	Low	High	Low	Low	High
2	Hannah Blau, 2001, Israel	High	High	High	High	Low	Low	Low
3	Siobhán B. Carr, 2018, UK	Low	Low	High	High	Low	Low	Low
4	Sumita Gupta, 2019, India	Low	Low	Low	Low	Low	Low	Low
5	Dominique Hubert, 2014, USA	Low	Low	Low	Low	Low	Low	Low
6	Kathleen (Kate) Zink, 2019, USA	Low	Low	High	High	Low	Low	High
7	Yuan-Chi Lin, 2005, USA	High	High	High	High	High	High	High
8	Jennifer Ruddy, 2015, USA	High	High	High	High	Low	Low	High
9	H.C.Selvadurai, 2001, Australia	Low	Low	High	High	Low	Low	High
10	Alan R. Smyth, 2009, UK	Low	Low	Low	Low	Low	Low	Low
11	Christopher McNamara, 2016, USA	High	Low	High	High	Low	Low	High
12	Annemarie Lee, 2008, Australia	High	High	High	High	Low	Low	High
13	N C, obanogÆ lu, 2002, Turkey	High	Low	High	High	Low	Low	High
14	Petra Rust, 2000, Austria	High	Low	Low	Low	Low	Low	High
15	S Renner, 2000, Austria	Low	Low	Low	Low	Low	Low	Low
16	Veronique Groleau, 2014, USA	Low	Low	Low	Low	Low	Low	Low
17	Johanna H. Oudshoorn, 2006, Netherlands	Low	Low	Low	Low	Low	Low	Low
18	Batia Weiss, 2009, Israel	High	High	High	High	Low	Low	High
19	L.C. Lands, 2009, Canada	High	High	High	High	Low	Low	High
20	DANA S. HARDIN, 2004, USA	Low	Low	High	High	Low	Low	High
21	Clésio Gontijo-Amaral, 2012, USA	Low	Low	Low	Low	Low	Low	Low
22	L. Hanssens, 2016, Belgium	Low	Low	Low	Low	Low	Low	Low
23	Vijaylaxmi Grey, 2003, Canada	Low	Low	Low	Low	Low	Low	Low
24	Marianne Skov, 2014, Denmark	High	Low	High	High	Low	Low	High
25	Nemat Bilan, 2019, Iran	Low	Low	Low	Low	Low	Low	Low
26	Stephanie Van Biervliet, 2018, Belgium	Low	Low	Low	Low	Low	Low	Low
27	A. DE ALESSANDRI, 2011, Italy	Low	Low	Low	Low	Low	Low	Low
28	Yasmeen Abu-Fraiha, 2018, Israel	High	High	High	High	low	low	High

ID	Study (First author, year, country)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
29	G. Alicandro, 2012, Italy	Low	Low	Low	Low	Low	Low	Low
30	Drucy Borowitz, 2011, Israel	High	Low	High	High	High	High	High
31	Wolfgang Bernhard, 2019, Germany	High	High	High	Low	Low	Low	Low
32	S P Conway, 2004, UK	High	High	High	High	Low	Low	High
33	Claudia de Castro-Silva, 2009, Brazil	Low	Low	Low	Low	Low	Low	High
34	Maiara Brusco de Freitas, 2017, Brazil	Low	Low	Low	Low	Low	Low	Low
35	Basilio De Vizia, 2002, Italy	High	High	High	High	Low	Low	Low
36	Lisa G Wood, 2001, Australia	Low	Low	Low	Low	Low	Low	High
37	Scott D. Sagel, 2010, USA	High	High	High	High	Low	Low	High
38	Christian P. Braegger, 2003, Switzerland	High	High	High	High	Low	Low	High
39	Jacqueline A. Jumpsen, 2006, Canada	High	High	High	High	Low	Low	High
40	Seyed-Ali Jafari, 2013, Iran	Low	Low	High	High	Low	Low	Low
41	Mansi Kanhere, 2017, USA	Low	Low	Low	Low	Low	Low	Low
42	Christina Keen, 2009, Germany	Low	Low	Low	Low	Low	Low	Low
43	Amanda Leonard, 2009, USA	High	High	High	High	Low	Low	High
44	John D. Lloyd-Still, 2005, USA	Unclear	Low	Low	Low	Low	Low	High
45	Valerie Marchand, 2000, USA	Unclear	Low	Low	Low	Low	Low	High
46	Vin Tangpricha, 2018, USA	Low	Low	Low	Low	Low	Low	Low
47	Gabriel Olveira, 2009, Spain	High	High	High	High	Low	Low	High
48	Vanessa J Poustie, 2006, London	Low	Low	High	High	Low	Low	Low
49	Pedram Ataee, 2014, Iran	Low	Low	High	High	Low	Low	Low
50	Ruth E. Grossmann, 2012, USA	Unclear	Low	Low	Low	Low	Low	High
51	T Pincikova, 2016, Sweden	Low	Low	High	High	Low	Low	High
52	Scott D. Sagel, 2018, USA	Low	Low	Low	Low	Low	Low	Low
53	Joan I. Schall, 2015, USA	Low	Low	Low	Low	Low	Low	Low
54	Gratiana Steinkamp, 2000, Germany	Low	Low	High	High	Low	Low	High
55	Matthew A. Tucker, 2019, USA	Low	Low	Low	Low	Low	Low	Low
56	S. Van Biervliet, 2007, Belgium	Low	Low	Low	Low	Low	Low	High
57	Ganesh Sharma DNB, 2016, India	Low	Low	Low	Low	Low	Low	Low

Different kinds of pain, including back pain, chest pain, and headache, were commonly seen among CF patients (19). These pains reduce the quality of life of these patients and are also associated with pulmonary exacerbations (73). Yuan-Chi Lin et al. (2005) measured the effect of acupuncture on pain management and achieved positive results (21).

Body techniques including Osteopathic manipulative treatment, summer camp, tai chi, exercise, yoga, physiotherapy, and massage were also applied. Notably, CF patients are at a higher risk of getting airway infections compared to the general population. Exercise can play important and key roles in improving the process of clearing lung secretions and reducing inflammation (74). Sumita Gupta et al. (2019) also found that exercise programs are not correlated with a significant improvement in bone marrow density (BMD) of CF patients, but it had a positive effect on both physical and mental health statuses of these patients (18). In another study, H.C.Selvadurai et al. found that the patients receiving aerobic training had significantly higher levels of peak aerobic capacity, activity levels, and quality of life compared to the control group (23).

Some beneficial effects of the dietary supplements and nutrition were also observed on the CF patients. Hanssens et al., for instance, examined the effects of long-term omega-3 supplementation on the number of exacerbations as well as the duration of antibiotic therapy in CF patients, and found several clinical benefits as a result (36). In another study, it was shown to have some positive effects like decreasing inflammation (49). Beta carotene was also found to have significant effects on pulmonary function and quality of life in CF patients (27, 28). Whey proteins were, further, indicated to improve nutritional status and they have additional beneficial effects on inflammation in patients with CF. They

also appear to have several potential immune-modulating effects that can be beneficial for CF patients over the long term (33).

Vitamin D supplementation may contribute to reduced inflammation and improved lung function in CF. It was found to be positively correlated with some changes in the adult Quality-of-Life respiratory score at the end of the supplementation (65).

The articles that examined the effect of antioxidants on CF manifested some improvements in the patients' weight and pulmonary function (50, 51, 66, 69). It was also demonstrated that an antioxidant cocktail can improve vascular endothelial function and oxidative stress in patients with CF, providing evidence that oxidative stress is a key contributor to vascular endothelial dysfunction in CF (69).

Moreover, the use of low-dose supplements of fatty acids over a long period (one year) appeared to improve pulmonary function, as well as the inflammatory and anthropometric parameters in adults with CF (61).

Likewise, The effects of zinc supplementation on CF patients showed good results, including significant increases in both height and weight and a decrease in the number of hospitalizations (63).

## 5- CONCLUSION

Although there is a great potential for using CAM techniques to manage cystic fibrosis, very limited evidence exists to support the use of CAM in the treatment of CF. Despite its widespread administration, such routine use cannot be supported by the existing research evidence; and more accurate data are required.

## 6- LIMITATIONS

Some of the articles studied in this systematic review had a low

methodological quality. Other limitations include high heterogeneity of the studies, resulting from the variety in the types of CAM therapies; and the small sample sizes in most articles indicating the need for further studies with larger sample sizes in this regard.

## 7- CONFLICT OF INTEREST

None.

## 8- ACKNOWLEDGMENT

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