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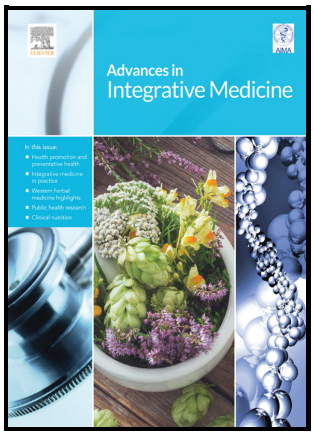

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PII: S2212-9588(23)00079-4

DOI: https://doi.org/10.1016/j.aimed.2023.09.002

Reference: AIMED360

To appear in: *Advances in Integrative Medicine*

Received date: 17 August 2022
Revised date: 10 August 2023
Accepted date: 3 September 2023

Please cite this article as: Nicole Hannan, Janet Schloss and Matthew J Leach, Safety and efficacy of complementary medicines for eosinophilic gastrointestinal disorders in adults: a systematic review and exploration of candidate interventions., *Advances in Integrative Medicine,* (2023) doi:https://doi.org/10.1016/j.aimed.2023.09.002

Safety and efficacy of complementary medicines for eosinophilic gastrointestinal disorders in adults: a systematic review and exploration of candidate interventions.

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Abstract

Eosinophilic gastrointestinal disorders (EGIDs) are a group of Th2-mediated antigen-driven conditions. The limitations of conventional management options (i.e. invasive monitoring,

adverse effects of pharmacological treatments and challenges with maintaining dietary restrictions) may lead people with EGIDs to seek other treatment options, such as complementary medicine (CM). Although there is mounting evidence supporting the safety and efficacy of some complementary medicines (CMs) for the management of gastrointestinal diseases, the evidence of effectiveness of CMs for EGIDs has not yet been systematically reviewed. A systematic review of controlled clinical trials and randomised controlled trials, including cross-over trials, examining the safety and / or efficacy of any CM, against any comparator, was conducted to determine the safety and efficacy of CMs in adults with EGIDs and to explore potential candidate interventions. The search identified 4,304 references. After title and abstract screening, 4,297 studies were excluded. The 7 identified studies were retrieved as full-text and assessed for eligibility. All 7 studies were excluded due to wrong study design (n = 1; retrospective study), and wrong patient population (n = 6; e.g. patients with functional dyspepsia or heartburn). No studies met the eligibility criteria for inclusion in this review. While there is a paucity of clinical studies examining the effectiveness of CM for EGID, findings from observational and experimental studies highlight possible directions for future research. These studies point to a number of CMs (i.e. nutritional supplements and herbal medicines) that show promise as a treatment for EGID; the clinical safety and efficacy of these interventions therefore warrants further investigation. Identifying safe, effective and acceptable treatment options for people living with an EGID may help to reduce disease and treatment burden in this population, and in turn, improve quality of life.

Keywords: Complementary Therapies; Efficacy; Eosinophilic Esophagitis; Eosinophilic gastrointestinal disorder; Gastrointestinal tract; Safety.

How did you gather, select and analyze the info you considered in your review?

- This systematic review examined the safety and / or efficacy of any complementary medicine, against any comparator, in adults with eosinophilic gastrointestinal disorders (EGID).
- Studies were identified using MEDLINE, AMED, CINAHL, Scopus, Google Scholar, Web of Science, clinical trial registers and the grey literature. The references of recent articles reporting on current management and treatment approaches for EGIDs were also searched for eligible studies.
- The search identified 4,304 references. After title and abstract screening, 4,297 studies were excluded. The 7 identified studies were retrieved as full-text and assessed for eligibility. No studies met the eligibility criteria for inclusion in this review.

What is the take-home message for the clinician?

- Many people with eosinophilic gastrointestinal disorders use complementary medicine.
- No trials have examined the effect of complementary medicine for these disorders.
- Some complementary medicines show promise for eosinophilic gastrointestinal disorders.
- The safety and efficacy of these promising complementary medicines warrants further investigation.

1 INTRODUCTION

Eosinophilic Gastrointestinal Disorders (EGIDs) are a group of Th2-mediated antigen-driven conditions characterised by elevated levels of eosinophils in the gastrointestinal (GI) tract (1, 2). Depending on the location of eosinophilic infiltration, EGIDs can be classified as eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic enteritis (EE), and eosinophilic colitis (EC) (3). The three latter conditions are often collectively referred to as eosinophilic gastroenteritis (EGE) (4)(5). However, recent nomenclature guidelines have suggested replacing the term “EGE” with "EGID" to better represent diseases of the gastrointestinal tract with pathologic eosinophilic infiltration in the absence of secondary causes (3).

The prevalence of EoE is estimated to range from 0.5-1 / 1,000 (6), increasing steadily with age until peaking between the ages of 30 and 44 years (6). EoE is most common in Caucasians (3, 7), males (3:1) (8), urban environments and Western countries (1, 6). First degree relatives of individuals with EoE are more likely to have EoE than the general population (which is higher in brothers, fathers and male relatives), and environment plays a stronger role than genetic heritability (9).

The prevalence of EGE is less clear due to the lack of recent prevalence studies, with estimates ranging from 5.1 to 28 per 100,000 population (1, 3, 10). Age data for EGE is also inconsistent, with one study indicating EGE is more common in children aged < 5 years (11), and another stating EGE is most common in persons aged 40-50 years (4). The prevalence of EGE appears to be higher in Asians than Caucasians (4, 7, 12), and slightly more common in males (1.2:1) (12, 13).

Chronic allergic reactions to food and environmental antigens are thought to be the main cause of EGIDs (3, 4, 14). In EoE, genetics, the environment (e.g. pollens, cold or dry climate), early antibiotic exposure and lack of early exposure to microbes are also thought to play a role (8). The aetiology of EGE is less certain, with many speculating food allergy as a possible cause (3).

EGID symptoms vary based on the extent of the tissue damage and the location of the disorder (3). Common manifestations of EoE in adults are dysphagia and food impaction; in other EGIDs, adults may present with nausea, vomiting, abdominal pain, diarrhoea, early satiety, and weight loss (3). This symptom burden is associated with reduced quality of life (QoL) in both adults (15, 16) and children (17, 18) with EoE. The reduced QoL, together with repeated invasive procedures, high healthcare costs, and strict elimination diets, contributes to a high burden of disease (16-20). The high prevalence of atopic disease in patients with EGIDs (11, 21, 22) may further add to the burden of EGIDs.

The conventional management of EGIDs typically focusses on identifying and eliminating dietary triggers, and controlling local inflammation and symptoms (3, 22). Adherence to elimination diets can be challenging however, particularly for those with multiple food triggers; the approach often also involves repeated invasive endoscopic monitoring (14). Corticosteroid medications and proton pump inhibitors (PPIs) are commonly prescribed for the management of EGID symptoms, but are associated with a range of adverse effects (e.g. renal disease, esophageal candidiasis, decreased bone mineral density, and hypothalamic-pituitary-adrenal-axis suppression) (23, 24); there is also a lack of evidence supporting the long-term safety and efficacy of these treatments in patients with EGIDs (4, 24). The

limitations of these conventional treatments may lead some patients to seek other treatment options, such as complementary medicine (CM)(17, 20).

Complementary medicines (25) are described as 'practices and products of non-mainstream origin' (26). The use of CM is common amongst individuals with chronic disease (27, 28) and GI conditions (29-31). However, there has been little research examining CM use in people living with EGIDs, particularly adults. A survey of Australian carers revealed a high level of CM use among children with EoE (20). Most carers indicated that CMs were effective in managing their child's EoE, with some reporting adverse reactions to CMs (17, 20). In most cases, carers self-prescribed CMs for their child's EoE, despite the lack of evidence for their safety and efficacy (20). Understanding the safety and efficacy of CM products is particularly important for EGIDs given the allergic nature of the disease.

In order to understand the potential role of CM in the management of EGIDs, and to identify key directions for future research, it is important to determine the state of the art. Although there is mounting evidence supporting the safety and efficacy of some CMs for the management of GI diseases (29), the evidence of effectiveness of CMs for EGIDs has not yet been systematically reviewed. Therefore, the purpose of this review was to determine the safety and efficacy of CMs for EGIDs in adults and to explore potential candidate interventions.

2 MATERIAL AND METHODS

2.1 DESIGN

A systematic review was conducted to determine the safety and efficacy of CMs for EGIDs in adults. The review was developed and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (32). The protocol was registered with PROSPERO (registration number CRD42021256786).

2.2 ELIGIBILITY CRITERIA

The review was limited to controlled clinical trials and randomised controlled trials (RCTs), including cross-over trials, examining the safety and / or efficacy of any CM, against any comparator in adults aged 18 years and over with EGIDs. Primary outcomes included: severity or intensity of GI symptoms (e.g. nausea, pain, dysphagia, diarrhoea), eosinophil levels (e.g. histologic, blood), and indicators of inflammation (e.g. urticaria, C-reactive protein, interleukin-5, immunoglobulin-G, Tumour-necrosis factor alpha). Secondary outcomes included QoL (including generic and disease-specific health-related QoL), severity or intensity of general symptoms (e.g. fatigue, anxiety), and adverse effects.

In this review, the term CM referred to two major domains: i) CM therapies (such as massage, yoga, acupuncture and meditation), and ii) CM products (33). CM products were defined as '*medicinal products containing such ingredients as herbs, vitamins, minerals, nutritional supplements, homoeopathic and certain aromatherapy preparations*' (34), and not by the purpose of usage (i.e. to address a vitamin deficiency) (35). Elimination diets or

elemental formula interventions were excluded as they are considered first line therapies for EGIDs, and not CM.

2.3 SEARCH AND SCREENING

Studies published/reported up to July 2022 were identified using MEDLINE (EBSCO), AMED (EBSCO), CINAHL (EBSCO), Scopus, Google Scholar, Web of Science, clinical trial registers (Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry) and the grey literature (ProQuest). The references of Hirano and Furuta (2020) (36), Gómez-Aldana, Jaramillo-Santos (2019) (37), Steinbach, Hernandez (2018) (14), and Dellon, Liacouras (2018) (22) were also searched for eligible studies as these recent articles report on current management and treatment approaches for EGIDs. The full search strategy can be found in supplementary material 1.

Search results were imported into EndNote™ X9. Removal of duplicates, title and abstract screening, and full text screening, were performed by NH using Covidence (Veritas Health Innovation, Melbourne, Australia). Using the accelerated approach, 20% of search results were randomly screened by ML and JS to confirm the accuracy of screening. Any disagreements were resolved by discussion.

2.4 DATA EXTRACTION & CRITICAL APPRAISAL

The authors planned to extract the following data from included studies: study details (author(s), year, title); Setting (including country and number of sites); Participants (including characteristics, sample size, inclusion / exclusion criteria); Design (including trial design, randomisation method, allocation concealment, blinding [participants, researchers, outcome assessors]); Intervention (including description, dose, duration); Control (including

description, dose, duration); Outcomes (including outcome measures and measurement time points); Adverse effects; Attrition rates; Exclusions; Use of appropriate power calculation and intention-to-treat (ITT) analysis; Protocol availability and comparison with final report; Trial registration; Grant support, and Conflict of interest.

NH planned to undertake the data extraction, with ML and JS cross-checking the accuracy of data. Any disagreements were to be resolved by discussion until consensus was reached. Corresponding authors of included studies were to be contacted if data / trial information were not reported in the publication. The Cochrane risk of bias tool for randomized trials (RoB 2) was the selected assessment tool for RCTs, and (38) the Joanna Briggs Institute (JBI) checklist for quasi-experimental studies (non-randomized experimental studies) tool was selected as the assessment tool for non-randomised studies (39).

2.5 DATA ANALYSIS

If two or more eligible studies were comparable in terms of CM product / therapy and outcome, data were to be pooled in a meta-analysis with Review Manager (RevMan) 5.4 software, using a random-effects model. To analyse the size of the effects of the interventions, mean differences (MD) and 95% confidence intervals (CI) were to be calculated for continuous data. For dichotomous data, effect sizes were to be expressed as relative risks with 95% CI. The authors planned to report heterogeneity by visual inspection of forest plots, and by using the I2 statistic. If data were not amenable to meta-analysis, they were to be analysed using narrative synthesis. The following subgroup analysis was planned if there were two or more eligible studies reporting the same CM product / therapy and outcome: (a) Effect of treatment duration (i.e. short-term, long-term) on primary outcome measures. In the event of an empty review, we will explore potential candidate

interventions to inform future research. These potential interventions will be identified via a systematic search of MEDLINE, AMED, CINAHL, Scopus, Google Scholar and Web of Science using the search terms outlined in supplementary material 1 with no limits to the study design.

3 RESULTS

Figure 1. PRISMA diagram for literature review on CM and EGIDs

<INSERT PRISMA DIAGRAM HERE>

3.1 RESULTS OF THE SEARCH

The database search identified 4,568 references (see **Error! Reference source not found.Error! Reference source not found.**). Following the removal of 264 duplicates, the remaining 4,304 references were screened against title and abstract, of which 4,297 studies were excluded. The 7 identified studies were retrieved as full-text and assessed for eligibility. All 7 studies were excluded due to wrong study design (n = 1; retrospective study), and wrong patient population (n = 6; e.g. patients with functional dyspepsia or heartburn). None of the studies met the eligibility criteria for this review. A search of clinical trial registries and the grey literature (ProQuest) identified 681 registered trials on EGIDs and 61 results respectively, of which none were eligible for this review. A single phase 2 pilot study investigating the efficacy of Fucoidan (a polysaccharide derived from seaweed) for EoE was identified, however the trial is ongoing with no publications available to date (40).

3.2 QUALITY OF INCLUDED STUDIES

No studies met the inclusion criteria for this review.

3.3 EFFECTS OF INTERVENTIONS

No studies met the inclusion criteria for this review.

4 DISCUSSION

The review identified no published clinical trials and only one active clinical trial assessing the safety and / or efficacy of CMs for EGIDs in adults. This is concerning given that the incidence and prevalence of these chronic and burdensome conditions are rapidly increasing (1, 3, 4, 6, 10, 11), and the use of CM in this population may be high (20, 27-31, 41). The concern is that many people with EGIDs report unmet health care needs (42, 43), and may turn to CM to address these needs (43), despite the lack of evidence supporting the clinical safety and efficacy of these interventions. Thus, in order to safeguard the public, there is a need to establish the safety and efficacy of CM interventions to aid patient and clinician decision-making.

The only known published clinical study examining the use of CM in adults with EGE (as identified through our search) did not meet the review inclusion criteria (i.e. the study was not a controlled clinical trial). In this retrospective clinical study (n = 40 adults), personalised traditional Chinese herbal medicine administered either orally or via enema was found to be comparable with prednisolone in reducing EGE clinical symptoms and rate of recurrence, with fewer adverse events and better patient compliance (44). Despite these promising findings, the study omitted important information on the methodology and results, deeming

the quality of this evidence as uncertain. A robust prospective, randomised controlled trial is now warranted to corroborate the findings of this retrospective study.

As there are no robust clinical studies examining CM use in adults with EGID, we drew upon a study of children with EoE to gain some insight into the types of CM interventions typically used in this population. The survey of CM use in children living with EoE revealed that 60% of children had used CM products and 23% had used CM therapies (20) to treat their EoE. The most commonly used CM products for EoE management were probiotics (43%) and nutritional supplements (41%) (20).

Probiotics are frequently used by children with EoE (20). Even though there is currently no evidence to support the clinical safety or efficacy of probiotics for EGIDs, there is some indication that GI dysbiosis may be present in people living with the disorder. Recent exploration of the GI microbiome in people with EGIDs has identified decreased *Clostridia* numbers in the gut (45), and increased *Haemophilus* levels in the saliva – both of which have been correlated with increased EoE disease activity (46). Furthermore, PPI therapy – a first-line treatment for EoE - has been associated with a reduced number of *Lactobacillus* species and gut dysbiosis (47).

Several probiotics show promise in addressing the dysbiosis observed in EGIDs; however, for probiotic use to be effective, it must be species, strain and disease specific (48). In a mouse model of EoE, *Lactococcus lactis* NCC 2287 was associated with significantly lower esophageal eosinophilia (p = 0.03) but only between days 28-38 of treatment (49). *Lactobacillus rhamnosus* GG (LGG) for EGIDs warrants further attention given that the strain increases the abundance of butyrate producing bacterial strains in the gut (50), reduces inflammatory cytokine-mediated decreases in intestinal epithelial barrier integrity (51, 52),

and improves IL-10 production (53). Additionally, LGG has been shown to improve GI symptoms (54) and tolerance to cow's milk protein (50, 55). However, it is important to note that although cow's milk protein is the most common trigger of EoE (8, 9), these findings were specific to IgE-mediated inflammatory responses, which are common in individuals with EoE, but are not specific to the known pathophysiology of the disease.

Short chain fatty acids (SCFAs), including butyrate, have been associated with reductions in eosinophil activation and migration, as well as associated inflammatory damage *in vitro* and *in vivo* (56). The prebiotic fibre inulin has been shown to improve SCFA and *bifidobacteria* levels in humans (57), and SCFA and *lactobacillus* levels in pigs, while also improving intestinal barrier function (58). Similarly, consumption of partially hydrolysed guar gum - another prebiotic fibre – has been associated with increased colonic SCFA production in human (59) and animal models (60), and reductions in intestinal inflammation.

Two of the most frequently used nutritional supplements among children living with EoE in Australia are iron and vitamin D (41). The use of these nutritional supplements in this population is not surprising given that iron and vitamin D deficiencies have been observed in patients with inflammatory gastrointestinal disease (61) and EGIDs (62-64). Recent experimental evidence has demonstrated that vitamin D receptor (VDR) activation inhibits fibroblast activation, thus alleviating intestinal fibrosis (65). Vitamin D has been proposed as a potential target for EoE therapy due to its ability to upregulate VDRs, resulting in downregulation of TGF-β, a profibrotic mediator implicated in the pathogenesis of EoE (66). Vitamin D may also assist in reducing eosinophil levels by modulating the eosinophil immune response (67, 68). This body of evidence suggests routine monitoring of iron and

vitamin D status, and appropriate supplementation, could play a part in the standard care for EGIDs, particularly in patients with substantial ongoing dietary restrictions.

It is important to consider the potential therapeutic efficacy of other nutrients targeting pathways known to be implicated in the pathogenesis of EGID. Many emerging treatments for EGIDs that are currently under investigation in clinical trials target specific immune response pathways involving mast cells (36). Mast cells are thought to play a role in the pathogenesis of EGIDs (69, 70) by altering esophageal smooth muscle contractility, and contributing to esophageal remodelling via production of TGF-β and other profibrotic factors (71, 72). Eosinophils have the ability to modulate the function of mast cells and *vice versa*; this bidirectional cross-talk facilitates further tissue damage in EoE and other chronic inflammatory conditions (73-75). Mast cells also secrete IL-5, which supports the activation and survival of eosinophils (75). While the use of mast cell stabilising pharmaceuticals is debated in EoE (22), they have been used successfully in EGE (76).

Quercetin is a plant-derived flavonoid with noted anti-allergic properties, including suppression of IL-4 and IL-8, mast cell stabilising effects, and the shifting of Th1 / Th2 balance towards Th1 (77-79). Animal studies suggest that the potent antioxidant and anti-inflammatory activity of quercetin may reverse inflammation in the gastrointestinal mucosa (80), and suppress eosinophil activation via downregulation of eosinophil chemoattractants (81, 82). While the effectiveness of quercetin has not yet been examined in patients with EGID, it has demonstrated antioxidant and anti-inflammatory effects in patients with other inflammatory / atopic conditions, such as rheumatoid arthritis (83), sarcoidosis (84) and asthma (85).

Topical application of Fucoidan, a marine polysaccharide derived from brown seaweeds, shows promise in the treatment for EoE due to its anti-inflammatory and antioxidant effects, with noted ability to reduce Th2 cell-mediated inflammation and eosinophil recruitment in animal models (86, 87). A single phase 2 pilot study investigating the efficacy of Fucoidan for EoE is currently underway (40).

Several herbal medicines also show promise as treatments for EGIDs, including *Curcuma longa* (Turmeric)*, Nigella sativa* (Black caraway) and *Scutelleria baicalensis* (Baical skullcap). Numerous experimental studies have explored the anti-inflammatory, anti-oxidant and immunomodulatory actions of *Curcuma longa*; these studies indicate the herb is able to modulate many of the inflammatory mediators associated with EGID (88). Furthermore, curcumin supplementation (Meriva®) has been shown to reduce pro-inflammatory mediators (CCL-2, IFN- γ, and IL-4), and promote a shift towards a healthy gut microbiome (increased *Lactobacillus* and *Clostridia* numbers, species potentially reduced in individuals with an EGID (47) (45)), in patients with chronic kidney disease (89).

Emerging evidence also supports the use of *Nigella sativa* in allergic and gastrointestinal disease (90-92). The volatile oil "Nigellone" has been shown to lower eosinophil levels and inhibit the release of histamine from gastric mast cells, thereby reducing gastric damage (91). However, caution must be exercised when using *N.sativa* as EoE is a Th2 dominant condition (93) and there is evidence to indicate that *N.sativa* aqueous extract may upregulate Th2 cytokine secretion (94). Compound 7, 4 Dihydroxy flavone (DHF), a flavonoid purified from licorice root (*Glycyrrhiza uralensis*), demonstrated the ability to inhibit eotaxin, Th2 cytokines, IgE, TNF-α, IL-6, and IL-8 in experimental models of EoE, highlighting its potential as a future therapeutic treatment (95).

Various herbal medicines have also demonstrated mast cell inhibiting or stabilising actions, most notably *S.baicalensis* (96-99). *S.baicalensis* also demonstrates anti-inflammatory and gastroprotective actions (96, 97, 100-103). In murine models, *S.baicalensis* has been shown to suppress Th2 mediated cytokine production (particularly IL-4 and IL-13), increase Th1 mediated cytokine production, reduce serum IgE and histamine, lower pulmonary eosinophil infiltration, and enhance intestinal barrier function (96, 100-102). Furthermore, in IL-4 and TNF-α stimulated human fibroblasts, *S.baicalensis* dose-dependently inhibited the production of the eosinophil-specific chemokine eotaxin (104). Although the safety of *S.baicalensis, C. longa,* and *N. sativa* have been established in healthy human subjects (105-108), further studies are required to support their efficacy, safety and use in adults with EGIDs.

5 CONCLUSIONS

This systematic review identified no prospective clinical trials examining the safety and / or efficacy of any CM for the treatment of EGIDs in adults. This is concerning given that many people living with an EGID may turn to CMs to manage unmet health care needs. Fortunately, findings from observational and experimental studies have revealed a number of CMs that show promise as a treatment for EGIDs. Future research is needed to (a) better understand treatment priorities for people living with EGIDs, (b) identify other potential treatments to address unmet needs in this population, and (c) establish the clinical safety and efficacy of promising treatments.

Funding

The project lead is supported by a Research Training Program (RTP) Scholarship funded by the Australian Government.

Conflicts of interest

The authors have no conflicts of interest to declare.

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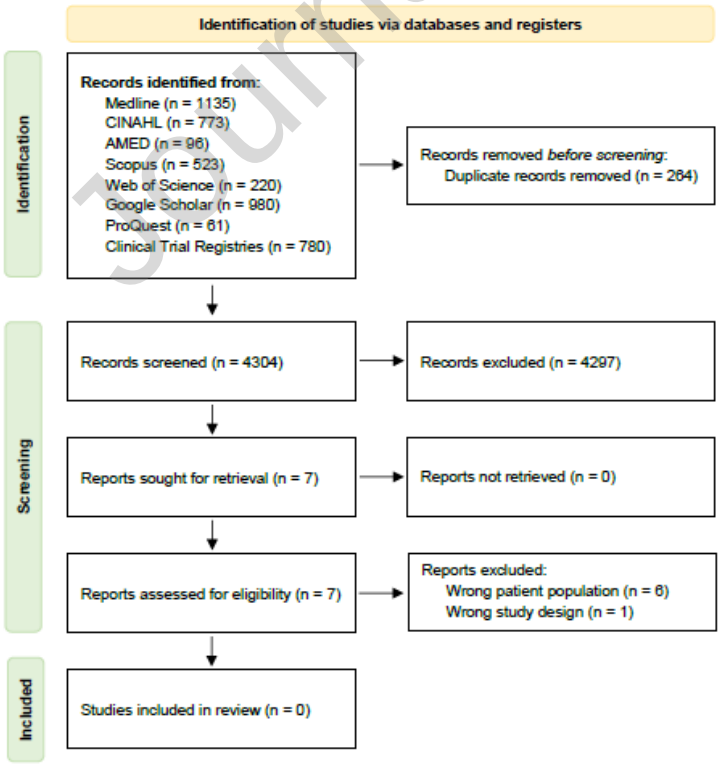
Figure 1. PRISMA diagram for literature review on CM and EGIDs



AUTHOR STATEMENT

This paper is our original work. We certify that this manuscript has not been published in part or whole elsewhere in any language, and it has not been submitted to any other journal for reviews. We certify that all authors named deserve authorship, and that all authors have agreed to be so listed and have read and approved the manuscript and its submission to AIMED. The authors have no conflicts of interest to declare.

The project lead is supported by a Research Training Program (RTP) Scholarship funded by the Australian Government.

Conflicts of interest

The authors have no conflicts of interest to declare.

Highlights

- Many people with eosinophilic gastrointestinal disorders use complementary medicine
- No trials have examined the effect of complementary medicine for these disorders
- Some complementary medicines show promise for eosinophilic gastrointestinal disorders
- Safety and efficacy of these complementary medicines warrants further investigation