Popular Remedies for Esophageal Symptoms: a Critical Appraisal

Amisha Ahuja[1] · Nitin K. Ahuja[2]

Abstract

Purpose of Review Popular remedies are of ongoing interest to patients experiencing common esophageal symptoms, particularly as typical pharmacologic interventions have been subject to increased scrutiny. Herein we summarize the available data regarding potential risks and benefits of several such remedies.

Recent Findings With emphasis on reflux and non-cardiac chest pain, research is ongoing into the clinical utility and diverse physiologic mechanisms underlying a variety of complementary and alternative modalities, including dietary manipulation, apple cider vinegar, melatonin, acupuncture, and various herbal products (rikkunshito, STW 5, slippery elm, licorice, and peppermint oil, among others).

Summary A substantial gap persists between anecdotal and empirical understandings of the majority of non-pharmacologic remedies for esophageal symptoms. This landscape of popular treatments nevertheless raises several interesting mechanistic hypotheses and compelling opportunities for future research.

Keywords Heartburn · GERD · NCCP · Diet · Nutrition · Complementary · Alternative · CAM

Introduction

It is tempting to limit our therapeutic purview to those interventions for which ample peer-reviewed data exist, but the reality of clinical care often entails navigating popular remedies pursued by patients alongside conventional treatments, with or without providers' explicit knowledge. This trend, which is true for medicine in general, also manifests in the specific context of esophageal disorders. A 2008 survey by the National Center for Health Statistics found that 38% of US adults report using some form of therapy that would be described as complementary/alternative medicine (CAM), while results of an online survey published in 2018 suggested that the rate of dietary supplement and CAM utilization among patients with gastrointestinal disorders was as high as 85% [1, 2•].

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✉ Nitin K. Ahuja
nitin.ahuja@pennmedicine.upenn.edu

[1] Department of Internal Medicine, Thomas Jefferson University, Philadelphia, PA 19107, USA

[2] Division of Gastroenterology, University of Pennsylvania, 3400 Civic Center Boulevard, 7 South Pavilion, Philadelphia, PA 19104, USA

Potential reasons why patients might be interested in alternative modalities are numerous [3]. Recalcitrant symptoms and rare diagnoses can leave conventional medicine lacking in data-based management options, in which case popular remedies sought independently by patients can seem poised to fill the gap [4]. Pre-existing health beliefs regarding the limits of Western medicine can also lead patients to seek out dietary and supplement-based solutions to gastrointestinal complaints, as can an aversion to the risk of medication side effects. Particularly among patients with esophageal symptoms, recent scrutiny on the potential negative implications of long-term proton pump inhibitor (PPI) use, amplified in popular media, can be difficult to neutralize despite thorough conversations regarding individualized risk/benefit ratios and statistical ambiguity [5].

Clinicians dealing regularly with foregut complaints, from general practitioners to dedicated esophagologists, thus have a vested interest in remaining familiar with popular remedies for esophageal symptoms and their putative mechanisms (Table 1). With humility to the systemic reasons for which complementary modalities are perpetually understudied, we also consider this review an opportunity to highlight topics for further organized research, to the extent that the anecdotal experience of patients and providers may be hypothesis-generating. Indeed, certain therapies that might have been deemed complementary in the recent past (e.g., hypnotherapy for non-cardiac chest pain,

Table 1 Selected popular remedies for esophageal symptoms

Intervention	Indication	Hypothetical mechanism(s)	Typical dose range (if applicable)
Dietary elimination	Heartburn/reflux	Decreased esophageal acid exposure, increased lower esophageal sphincter tone	n/a
Dietary fiber supplementation	Heartburn/reflux	Decreased esophageal acid exposure	n/a
Apple cider vinegar	Heartburn/reflux	Downregulation of endogenous acid production	Small amount (e.g., 1 teaspoon) diluted in water after meals
Melatonin	Heartburn/reflux	Enhanced mucosal barrier protection	3–6 mg daily
Rikkunshito	Heartburn/reflux, dyspepsia	Decreased esophageal acid exposure, foregut prokinesis	7.5 g daily
STW 5	Heartburn/reflux, dyspepsia	Regional foregut prokinesis, decreased acid production, decreased inflammation	10–20 drops with meals
Slippery elm	Heartburn/reflux	Mucosal protection via mucilage	Various
Licorice derivatives	Heartburn/reflux	Mucosal protection via raft formation	Various
Peppermint oil	NCCP	Smooth muscle relaxation	Various
Acupuncture	Heartburn/reflux, NCCP	Stress reduction, decreased visceral hypersensitivity	n/a

n/a not applicable

alginate derivatives for gastroesophageal reflux disease [GERD]) have, through rigorous study, found secure purchase in the management algorithms of conventional medicine.

Reflux

GERD is a common disorder in the USA and worldwide, with a prevalence between 18 and 28% in North America that has been rising over the past few decades [6]. Mainstays of GERD therapy include behavioral modification, acid-suppressing medications (most commonly PPIs and histamine-2 receptor antagonists [H2RAs]), and anti-reflux surgery in refractory cases. Particularly given recent attention to the potential adverse effects of long-term use of acid-suppressing drugs, there is growing interest among patients in ways to liberate from traditional pharmacologic approaches.

As a diagnosis that suggests a pathologic burden of acid exposure to the distal esophagus, GERD should be distinguished from symptoms of heartburn and regurgitation, which are often attributed presumptively to acid reflux but may also be caused by a variety of other disease processes, including non-acid reflux, esophageal hypersensitivity, functional heartburn, and esophageal motility disorders. Given that patients with symptoms suggestive of GERD may never undergo diagnostic testing to confirm this diagnosis, the anecdotal enthusiasm for various popular reflux remedies is perhaps more correctly understood as oriented toward heartburn. While reflux is perhaps the most common esophageal complaint for which alternative remedies have been popularized and sought, it is not always isolated or well-defined.

Dietary Modification

Among the general behavioral maneuvers typically recommended for mitigating GERD symptoms, those with a reasonable basis of evidence and which are recommended by professional guidelines include weight loss, late-night meal avoidance, and head of bed elevation [7, 8]. A variety of specific foods are commonly regarded as triggers for reflux symptoms, though the data supporting these associations tend to be scant and indirect. Carbonated beverages, chocolate, and foods high in fat have been shown to decrease the pressure of the lower esophageal sphincter, suggesting a potential mechanism whereby reflux symptoms could be provoked. Alcohol, chocolate, and foods high in fat have also been shown to increase esophageal acid exposure times, again suggesting a possible explanation for increased reflux symptoms [9]. Citrus products, tomato products, spicy foods, and other caffeinated beverages (e.g., tea) are also commonly cited by patients with heartburn as provocative factors [10, 11]. That said, there are no published trials proving that avoiding putative trigger foods improves reflux symptoms, for which reason professional guidelines advise against their routine exclusion [7].

Further attention has been paid lately to carbohydrates as potential mediators of reflux symptoms. In a study of 144 obese women, for example, 42 of whom had a baseline GERD diagnosis, institution of a high-fat, low-carbohydrate diet led to significant reductions in reflux symptoms and associated medication usage after 16 weeks [12]. Notably, this finding challenges the putative association between dietary fat and reflux exacerbation outlined above. An older study of 8 obese patients placed on a low-carbohydrate diet noted similar symptomatic improvement that correlated with reductions in esophageal acid exposure via formal pH testing performed after 1 week [13]. Separately, fiber supplementation has been found to be associated with reductions in reflux symptoms, including in a recent study of 36 patients with non-erosive reflux disease and low baseline dietary fiber consumption, though it had no effect on objectively measured esophageal acid exposure [14]. Of course, carbohydrate restriction has become a popular undertaking lately for reasons unrelated to GERD, including weight loss in the context of contemporary diet trends and the treatment of abdominal distress in the context of irritable bowel syndrome [15]. In certain individuals,

therefore, it may be that reported improvements in reflux symptoms are attributable to or confounded by improvements in adjacent conditions.

Recent cross-sectional studies have identified a variety of specific dietary components whose intake appears to be associated with a relative reduction in reflux symptom prevalence, including fruits, vegetables, seaweed, milk, fish, and beans in a Korean cohort, and miso soup in a Japanese cohort [16, 17]. In the same Korean cohort, a reduced likelihood of non-erosive reflux disease was associated with high intake of particular micronutrients, including calcium in men and vitamins A, B2, B6, folate, calcium, and iron in women [18]. Recognizing that these studies are subject to significant interpretative limitations by virtue of their methodology, they suggest intriguing hypotheses on which to predicate future research into dietary modification strategies. Fruits, vegetables, and beans constitute high-fiber foods, for example, while miso was posited by its investigators to protect against reflux by accelerating gastric emptying [19].

Apple Cider Vinegar

Apple cider vinegar (ACV) is a particularly popular remedy for reflux symptoms and an especially counterintuitive one for many clinicians given its acidic composition (and thus its proximity to other commonly reported GERD triggers like tomatoes and citrus). Indeed, acetic acid (the active ingredient in vinegar) is considered toxic at concentrations higher than 20% given the risk of caustic injury to the esophageal mucosa, noteworthy for patients who are independently pursuing this remedy in an often poorly regulated consumer market [20, 21]. ACV has also been shown to slow gastric emptying, a quality that would seem to predispose to worsened rather than improved reflux symptoms [22]. Nonetheless, several individuals attest to deriving benefit from ACV, often to the exclusion of other vinegar products, for reflux symptoms on an anecdotal and longitudinal basis.

While published evidence suggests that ACV can reduce blood glucose levels, improve lipid profiles, and impede the growth of certain microbes, data on the particular utility of ACV for reflux symptoms are almost nonexistent [23, 24]. A small, 2-week trial of a proprietary gum product containing ACV, licorice, and papain (an enzyme derived from papaya) noted improved postprandial reflux symptom scores when compared against placebo gum. The effects of ACV are difficult to separate from the gum's other components, however, and its application as a gum seems qualitatively different from the more popular mode of ingestion (often a small amount of ACV diluted in water and drunk after meals) [25]. An unpublished graduate thesis from 2015 addressed the question more formally, recruiting 15 individuals (of whom 7 were deemed appropriate for final analysis) to a randomized sequence of study meals containing typical reflux triggers with or without

a subsequent dose of over-the-counter antacids or diluted ACV. No significant improvement in heartburn scores was noted in the comparison between the control meal and the experimental addition of antacids or ACV, though the study was underpowered [26].

By what mechanism is ingestion of an acidic compound supposed to reduce symptoms of acid reflux? A few speculative models have been put forward, though again without much evidence to support them. For instance, a 2018 study of 130 patients selected according to an endoscopic diagnosis of reflux or gastritis found that the restriction of specific carbohydrates (glycines) iteratively supplemented with acidic foods (lemon juice and fresh tomato) led to improvements in symptoms of reflux, eructation, upper abdominal distension, and mucous production. While the study's inclusion criteria and outcome metrics are atypical for GERD, the authors interpret their intervention as acid suppressive in nature, speculating that ingested acid might function to downregulate endogenous acid secretion by a negative feedback mechanism [27]. More general lay conceptions of corporeal "pH balance" can lead some patients to presume reflux symptoms to arise from hypochlorhydria, a faulty intuition that may be reinforced by alternative practitioners and that might lay groundwork for a placebo response [28].

Melatonin

Melatonin is an endogenously produced hormone that is perhaps most commonly associated with sleep-wake cycle regulation, though there is also interest in the potential utility of exogenous melatonin supplementation for the treatment of GERD. Melatonin produced by foregut gastrointestinal tissues has been posited by some investigators as strengthening mucosal barrier function against esophageal irritation by acid reflux, and even more speculatively, protecting against the development of intestinal metaplasia and cancer [29]. Setting aside this bolder latter hypothesis, clinical data from case reports and small trials suggest some potential for symptomatic benefit in GERD. A 2010 study that randomized 27 GERD patients to therapy with either 3 mg melatonin daily, 20 mg omeprazole daily, or a combination of the two found that heartburn symptoms resolved completely in all groups after 8 weeks, leading them to conclude that melatonin might be a viable treatment option for GERD, alone or in combination with PPIs. Interestingly, the study also found that baseline melatonin levels in GERD patients were consistently low in comparison to age- and sex-matched controls [30]. A 2006 study randomizing 351 patients with heartburn to treatment with either 20 mg omeprazole daily or a combination of 6 mg melatonin plus various supplemental vitamins (L-tryptophan, a melatonin precursor; vitamin B6; folate; vitamin B12; methionine; and betaine) over 40 days noted significantly more frequent symptom resolution in the melatonin/supplement arm than in the

omeprazole arm (100% versus 65.7%) [31]. Notably, the protocol advised participants to administer the study drug after meals, in contrast to usual PPI dosing recommendations.

Rikkunshito

Rikkunshito is a traditional Japanese therapy comprised of 8 herbal extracts (*Atractylodis lanceae rhizoma*, *ginseng radix*, *pinelliae tuber*, *hoelen*, *zizyphi fructus*, *aurantii nobilis pericarpium*, *glycyrrhizae radix*, and *zingiberis rhizoma*) that has been utilized historically for a variety of digestive symptoms. A recent meta-analysis identified and aggregated 24 studies of rikkunshito from 1990 to 2018 (dosed consistently at 7.5 g daily) and, despite significant heterogeneity in symptom focus, comparator arms, and outcome measures, noted significant improvements in appetite and upper gastrointestinal symptoms using a 5-point scale [32•]. Among these individual studies, a few focused particularly on reflux. A 2012 study of 104 patients with PPI-refractory GERD symptoms found that a 4-week combination of rikkunshito with 10 mg rabeprazole daily was similar to double-dose (20 mg daily) rabeprazole in the degree of symptom improvement noted [33]. A larger 2014 study (G-PRIDE) by the same group yielded no significant difference, however, in its comparison of combination rikkunshito and rabeprazole therapy with rabeprazole alone [34]. Separately, a study of 8 children (6 of whom were neurologically impaired) with symptomatic reflux found that 1 week of rikkunshito reduced symptoms and esophageal acid exposure time as measured by 24-h pH/impedance testing [35].

As with other compounds comprised of multiple herbal components, it is difficult to distinguish rikkunshito's active ingredients from its inert ones or to identify a single, discrete mechanism of action. That said, given the compound's more pronounced benefits in dyspepsia trials, along with findings from animal studies of serotonin receptor agonism and ghrelin potentiation, the prevailing assumption is that rikkunshito operates primarily as a foregut prokinetic [36]. This hypothesis concords with findings from a secondary analysis of the G-PRIDE study suggesting that elderly patients with an overlap of reflux and dyspeptic symptoms were particularly poised to benefit from rikkunshito. The meta-analysis mentioned above noted no significant adverse events related to rikkunshito and no significant difference in reported adverse events in relation to its various study comparators. It bears mentioning, though, that standard preparations of rikkunshito are not easily obtained outside Japan, suggesting that poorly regulated substitutes could be associated with higher risk profiles.

STW 5

STW 5 is a compound of 9 herbal extracts (garden angelica root, milk thistle fruit, caraway fruit, greater celandine, bitter candy tuft, licorice root, German chamomile flowers, lemon balm leaf, and peppermint leaf) originally developed in Germany (marketed as Iberogast®), likewise used for a variety of foregut symptoms but principally dyspepsia. While specific data for the compound's utility in reflux are scant, a 2004 meta-analysis noted that benefit in dyspepsia seemed to be more pronounced in patients with associated GERD symptoms [37]. Proof of concept for therapeutic action against GERD was suggested by a 2010 study in which rats pretreated with STW 5 demonstrated dose-dependent reductions in acute esophagitis severity following surgical foregut ligation (though the external validity of this disease model is clearly limited) [38]. The presumptive mechanism of STW 5 is multifactorial, with various studies suggesting regional effects on gastrointestinal motility, attenuation of gastric acid secretion, and generalized anti-inflammatory effects [39]. The safety profile of STW 5 is quite favorable, with a reported adverse event incidence of 0.04% [40]. While individual components of the compound preparation have been idiosyncratically associated with toxicity at high doses (e.g., liver injury following use of greater celandine extract), these reactions have not been reported with STW 5 at usual doses [41].

Slippery Elm

Slippery elm is a botanical product derived from the bark of the slippery elm (*Ulmus rubra*) tree, with anecdotal benefits reported for a variety of symptomatic complaints, including reflux. Slippery elm tends to be formulated in capsules, lozenges, and liquid preparations, including teas. Its presumptive mechanism in reflux relates to mucilage, a set of constituent carbohydrates that becomes viscous in contact with water, theoretically serving as a protective coating to luminal mucosa. A pilot study of 24 healthy volunteers randomized to either slippery elm tea or a placebo herbal tea reported a relative increase in a subjective sense of "throat soothing" with the former, though the trend did not reach significance. Experimental data for GERD symptoms are otherwise lacking, though this putative mechanism parallels that of sucralfate and alginate derivates, with the caveat that slippery elm's viscous transformation is not contingent on an acidic milieu. Risks include miscarriage, which necessitates avoidance among women who are or may become pregnant [42].

Licorice

Licorice (alternately spelled liquorice) is a herbal product that has been used on a longstanding basis for a variety of somatic symptoms, with interest in recent years shifting toward certain chemical derivatives. Glycyrrhizin is one of the primary components of licorice and has been studied primarily in the context of gastric ulcer healing, with optimistic results reported in small animal studies [43]. The clinical utility of glycyrrhizin for

reflux is not well established and is limited by a toxic metabolite that can exert potent mineralocorticoid effects, leading acutely or chronically to hypertension, muscle weakness, metabolic alkalosis, and even death [44]. Deglycyrrhizinated licorice (DGL) is a form of licorice in which glycyrrhizin has been removed in order to mitigate its toxicity profile and likewise has been studied primarily in the context of ulcer healing, with variable results [45, 46]. One recent investigation of DGL raised the possibility of benefit for reflux symptoms, though GERD was not well distinguished from dyspepsia within the small study population, and the licorice derivative was administered in combination with peppermint and slippery elm [47]. Carbenoxolone is a synthetic derivative of glycyrrhizin that is a raft-forming agent with a mode of action similar to alginates, forming a polymer that functions as a mechanical reflux barrier. Along with antacids, carbenoxolone was a popular choice for the treatment of acid-related disorders prior to the advent of H2RAs [48]. The most useful data reviewing this agent are decades old but demonstrate additive benefit over antacids and alginates alone in symptomatic relief and endoscopic healing of reflux esophagitis [49]. Licorice root extract remains commercially available, including as a component of STW 5 as noted above, though it is unknown to what extent this formulation shares any of the observed benefits of its various derivatives.

Other Herbal Products

A few other herbal compounds have yielded limited results from small, exploratory studies. For instance, a proprietary extract of fenugreek was evaluated in a 2-week randomized controlled trial ($n = 45$) and found to be superior to placebo and similar to ranitidine 75 mg twice daily in mitigating heartburn symptoms [50]. In a separate animal study, Chinese honeysuckle (*Lonicerae flos*) extract demonstrated dose-dependent attenuation of acute esophagitis following foregut ligation in rats, but again, it is difficult to extrapolate these findings clinically [51]. Belladonna, the plant from which atropine was derived, is sometimes used as a tincture by naturopathic practitioners to treat GERD [52]. While there is experimental evidence to suggest that atropine might reduce reflux burden by inhibiting transient relaxations of the lower esophageal sphincter, the botanical extract has not been studied and is certainly associated with the risk of anticholinergic side effects [53]. Honey has been posited as a potential reflux remedy as well on the basis of previously demonstrated antioxidant effects as well as its native properties of viscosity and density that lead to prolonged mucosal contact, but these presumptive mechanisms remain speculative [54]. Anecdotal reports suggest benefit with a wide range of other herbal products, including individual components of the compound preparations discussed above (e.g., chamomile and angelica root) and others (e.g., ginger root, marshmallow root, rosemary leaf,

turmeric, and aloe), though to our knowledge, the use of these particular botanical interventions for reflux remains formally unstudied [52, 55].

Non-cardiac Chest Pain

Non-cardiac chest pain (NCCP), discomfort analogous to angina pectoris in the setting of a negative cardiac evaluation, is a symptom with multiple potential causes, some of which are related to the foregut. It is a relatively common symptom, with some studies suggesting a prevalence of up to one third of the general population [56]. Among esophageal causes of NCCP, GERD is thought to be the most common, although the mechanism by which the disease causes chest pain is poorly understood (and complicated by the fact that some patients experience heartburn and chest pain symptoms independently) [57]. Aside from GERD, presumed esophageal causes of NCCP include esophageal dysmotility (including spastic esophageal disorders and hypertonicity of the lower esophageal sphincter) and visceral hypersensitivity. Conventional management of GERD-related NCCP favors acid suppression therapy, while for NCCP unrelated to GERD, approaches tend to favor neuromodulatory agents, calcium channel blockers, botulinum toxin, and/or hypnotherapy [58]. Many patients continue to suffer from NCCP despite usual interventions, however, and certain medication classes may be poorly tolerated, which can inspire pursuit of other popular remedies for symptom management.

Peppermint Oil

Peppermint oil, a popular treatment option for a variety of gastrointestinal concerns (e.g., functional dyspepsia and irritable bowel syndrome), is presumed to work via its menthol component as a smooth muscle relaxant. By extension, it is hypothesized that peppermint oil might also alleviate NCCP by reducing hypercontractility and/or spasm. A small study evaluating the effects of peppermint oil on 8 subjects with a manometric diagnosis of diffuse esophageal spasm provided proof of concept for this hypothesis, noting an improvement in simultaneous contractions 10 min after peppermint oil ingestion. It should be mentioned that the study subjects had symptoms of either dysphagia or chest pain rather than NCCP alone and that there was no attention in this study to clinical improvement related to this intervention [59]. Likewise, manometric findings vary significantly among patients with NCCP, limiting the applicability of these results to NCCP at large.

A more recent study evaluating 38 patients with either NCCP or non-obstructive dysphagia found that the use of oral peppermint oil tablets improved symptoms in a majority (63%) with no patients reporting worsening symptoms after the intervention. Greater improvement was seen in patients with NCCP and particularly in those with esophageal motility disorders, again suggesting a reasonable basis for the benefit

of peppermint oil in this clinical context [60•]. It should be noted that peppermint is often considered to be a reliable dietary trigger for reflux, suggesting that NCCP that is mediated by GERD could in theory be worsened through the use of this intervention [61]. In general, however, its harm profile is minimal.

Acupuncture

Acupuncture, a longstanding modality within traditional Chinese medicine, has become increasingly accepted as a therapeutic intervention among Western clinicians and patients alike. A study conducted among 235 patients with NCCP, for example, demonstrated that approximately half of the group would be open to trying acupuncture in the treatment of their symptoms [62]. There are several adjunctive modalities that can be used to modify the stimulation applied across acupuncture needles, including physical manipulation, electrical pulse generation, and heat application, with each likely meriting independent study [62]. Despite acupuncture's long history as a therapeutic intervention, there are comparatively little data available for its effects on NCCP in particular.

Among the reasons why acupuncture might benefit patients with NCCP is a potential connection to improvements in reflux disease. For example, a 2007 study of 30 patients with classic reflux symptoms on PPI therapy found that adding acupuncture was more effective than doubling the PPI dosage in reducing heartburn symptoms over 4 weeks [63]. A recent meta-analysis of 12 randomized controlled trials reinforced these findings, demonstrating that a combination of acupuncture with conventional Western GERD management was superior to the latter alone [64]. Another potential mechanism for acupuncture's efficacy is as a modality for reducing stress, a potential contributor to symptoms in patients with NCCP. A correlation between NCCP and psychological distress has been demonstrated in the past, though the direction of causality between these two variables is not well established [65]. Finally, acupuncture may have benefits for mitigating visceral hypersensitivity, as suggested by thematically related studies of transcutaneous electrical nerve stimulation demonstrating that the intervention reduces sensitivity to esophageal distension [66].

Conclusion

Esophageal complaints like reflux and non-cardiac chest pain may drive patients to seek out popular remedies for a number of reasons, from the failure of conventional, first-line interventions to concerns regarding medication side effects. Particularly for signs and symptoms with a broad differential diagnosis, patients should be aware of the importance of a thorough diagnostic workup if not already performed. That said, providers are likely to be well-served by literacy with the landscape of popular treatment options for common esophageal symptoms and the extent to which their associated evidence basis is negative, anecdotal, or cautiously optimistic. The attraction to popular remedies is likely to persist in the future, a forecast that encourages further research to better clarify the safety, reliability, and plausibility of these interventions' effects.

Compliance with Ethical Standards

Conflict of Interest   The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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