

Treatments for Recurrent Aphthous Stomatitis

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Abstract

Recurrent aphthous stomatitis (RAS) is a common condition in the Western world, and the condition is one that is not especially responsive to conventional treatments. Although poorly researched, there are many botanicals that have a long history of use in traditional medicine. These remedies, combined with dietary and other changes, are reportedly able to both soothe an acute outbreak as well as preventing recurrences. The remedies are benign, and practitioners should be comfortable using them while, we hope, these herbs are studied further to determine the extent of benefit they provide for patients with this condition.

Rhodiola rosea (rhodiola) root, *Glycyrrhiza* spp. (licorice) root, *Coptis* spp. (goldthread) root, *Coptis chinensis* (*huang lian*) root, *Phytolacca americana* (poke root), *Eupatorium laevigatum* (eupatorium; now frequently called *Chromolaena laevigata*) herb, *Alchemilla vulgaris* (lady's mantle) leaf, *Myrtus communis* (myrtle) leaf, *Spilanthes acmella* (toothache plant) herb, and *Echinacea* spp. (purple coneflower) root or herb are all discussed as potential treatments in this article.

Introduction

Recurrent aphthous stomatitis (RAS), also known as canker sores, is a common condition in the Western world. As one commentator said, discussing the relative ineffectiveness of conventional treatment, “[t]he best that can be achieved is to avoid local traumatic precipitants, lessen the pain and duration of ulceration by suppressing the local immune response, and prevent secondary infection.”¹ Although poorly researched, there are botanicals that have a long history of use in tradi-

tional medicine for aphthae. These remedies, combined with dietary changes, can both soothe acute outbreaks, which can cause substantial discomfort, as well as preventing recurrences. The remedies are benign and practitioners should be comfortable using them while further studies are conducted to determine the extent of benefit these remedies provide.

Forms and Frequency of RAS

RAS causes recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or gray floors. Often, multiple sores occur at the same time and usually begin to appear in childhood or adolescence. These ulcers are painful and frequently interfere with speech and eating. RAS differs from cold sores caused by the herpes simplex virus. The latter usually occur at the edge of the lips, but can also affect the “attached” tissues inside of the mouth, such as the hard palate and the gingiva. In contrast, RAS outbreaks occur on the loose tissues inside the mouth—such as the soft palate, tonsils, buccal mucosa, and underside of the tongue—and have not been shown to be caused by a virus (although this is still under investigation). We covered botanical treatments for cold sores in a previous article.²

RAS is divided into three groups: minor; major; and herpetiform. About 80% of patients are categorized as having minor RAS when the ulcers are less than 5 mm in diameter. The ulcers typically do not occur on the gingiva, palate, or dorsum (back or posterior) of the tongue and usually heal within 10–14 days without scarring. Major RAS is rare and severe, with ulcers larger than 1 cm that are oval. The ulcers tend to occur on the lips, soft palate, or fauces (between the back of the mouth and the pharynx), may persist for up to 6 weeks, and often result in scarring. Outbreaks are chronic and can last for more

than 20 years. Herpetiform RAS is yet rarer and is characterized by multiple recurrent crops of small, painful ulcers. There may be as many as a hundred ulcers at a time, each being 2–3 mm although they may fuse to form large irregular ulcers. This type of RAS appears to be more common in women and tends to have an onset at an older age.

Minor RAS is quite common and occurs with greater frequency in certain groups of patients. Thus, it was found in 60% of female student nurses, 56% of male student dentists, and 55% of professional-school students. The lowest incidence in this study of medical professionals and patients was found in male patients, of whom 5% had RAS. RAS is reportedly most common in North America, with a predominance in women, children, and Caucasians. About 1% of children have recurrent oral ulcers, but up to 35%–40% of American children have a history of RAS-like disease. Children with a higher socioeconomic status are more commonly affected than children from a more-impooverished background.

Dietary Factors in RAS

Food Sensitivities

Wheat and related grains contain a group of proteins—commonly referred to collectively as gluten—that are not tolerated by individuals with celiac disease. This ailment is on the rise or at least it is being recognized as more common than previously thought. In addition, subclinical or atypical celiac disease is increasingly diagnosed. Although the data are incomplete and somewhat contradictory, there are indications that a wheat-free diet may relieve RAS in some individuals. Moreover, the presence of RAS may be the sole symptom of celiac disease, a symp-

quent in the celiac group (22.7% versus 7.1%). Patients with celiac disease on a gluten-free diet significantly improved when reevaluated a year later (71.7% reported no or reduced episodes of RAS).³

There are other studies contradicting these findings. Some studies conclude that celiac disease does not manifest as RAS to any significant extent.⁵ As a result, conventional medicine generally rejects any association between wheat consumption and RAS. Usually, these rejections are primarily based on the claimed difficulty of eliminating gluten from the diet rather than on reliable data showing a lack of benefit when gluten is removed from the diet.

There are a number of studies suggesting that RAS may indicate celiac disease and that recommend that patients with RAS be tested and/or treated for it. One study evaluated 42 patients with RAS and 42 controls. While the correlation between RAS and celiac disease was low (4.7%), RAS symptoms responded well to a gluten-free diet, and the researchers concluded that their results merited the recommendation that patients with RAS and gastrointestinal (GI) complaints be screened for markers of celiac disease.⁶

On occasion, RAS may be the sole manifestation of gluten sensitivity. One study tested 247 patients with RAS, each of whom had at least 3 aphthous attacks a year. Seven of the 247 patients tested positive and none had responded to conventional treatments (topical corticosteroids, tetracycline, and colchicine). A wheat-free diet reduced RAS in 4 of the 7 patients. The researchers concluded that patients who were unresponsive to RAS treatments should always be investigated for gluten intolerance.⁷

Furthermore, there are many cases of subclinical celiac disease in patients whose RAS is reduced when a gluten-free diet is adopted. In addition, both confirmed and subclinical/silent celiac disease are increasing in incidence. One study looked at a group of 252 patients referred for GI symptoms. Of these patients, 57.14% were diagnosed with celiac disease and 42.86% were diagnosed with subclinical/silent disease. RAS was found in 5.68% of patients with subclinical disease.⁸

In our practice, many patients without established celiac disease improve greatly when gluten-containing grains are eliminated from their diets. Given the increased availability of gluten-free foods and the benefit that can accrue, we recommend that patients should eliminate gluten-containing grains from their diets as one aspect of an appropriate treatment for RAS.

While less-studied than wheat in RAS, dairy food is also a potential causative factor in RAS recurrence that also deserves to be explored. Thus, one study looked at gliadin and cow's milk protein sensitivities in patients with RAS. No correlation was found with gliadin, but there was a strong association between RAS and high levels of immunoglobulin A (IgA), IgG, and IgE antibodies to cow's milk protein.⁹ Other foods that may play a role in RAS include chocolate, coffee, peanuts, almonds, strawberries, and tomatoes.¹⁰

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RAS may occur more frequently in gluten-sensitive individuals, and a number of these people report no or reduced episodes of aphthous ulcers after adhering to a gluten-free diet.³ One study compared 197 patients with celiac disease with 413 controls. Forty-two percent of the patients with celiac disease had oral lesions compared to 2% of the controls. RAS disappeared in 89% of the patients with celiac disease after a year on a gluten-free diet. Despite the benefit of treatment, the positive-predictive value of these lesions for celiac disease was low.⁴

In another study, 269 patients with celiac disease (confirmed serologically and histologically) were compared with a control group of 575 healthy volunteers. RAS was much more fre-

Dose Chart

Herb	Part	Form	Dose
<i>Rhodiola rosea</i>	Root	Capsule	200 mg/day
<i>Glycyrrhiza glabra</i> , <i>G. uralensis</i>	Root	Young children: Tea Adults/older children: DGL tablets	1 rounded tsp/cup of water, not simmered more than 3–4 minutes to avoid bitterness. Chewed or dissolved in warm water as needed.
<i>Coptis</i> spp., <i>Hydrastis canadensis</i>	Root	Tincture only	Diluted in water and applied topically to ulcers
<i>Mahonia aquifolium</i>	Root	Tincture or tea	Applied topically to ulcers as needed
<i>Spilanthes acmella</i>	Flower	Tincture or tea	Applied topically to ulcers as needed
<i>Alchemilla vulgaris</i>	Leaf	Glycerite, tincture, or tea	Applied topically to ulcers as needed
<i>Myrtus communis</i>	Leaf	Powder	Mixed with water to form paste and applied topically to ulcers as needed

DGL, deglycyrrhizinated form of licorice.

Dietary Deficiencies

A general dietary workup needs to be part of any treatment plan for RAS. Up to 20% of patients with RAS have shown a deficiency in important nutrients, with deficiencies in iron, folic acid, and vitamins B₆ and B₁₂ being twice as prevalent in patients with RAS.¹¹ However, some scientists caution that these deficiencies may be unimportant as supplementation to address these deficiencies purportedly seldom resolves RAS.¹ Of course, it is possible that overcoming deficiencies combined with other approaches may help resolve RAS.

Stress and RAS

Stress appears to be an important factor in the etiology of RAS.^{12*} Again, however, conventional medicine, for the most part, simply dismisses the benefits of stress reduction as unproven. Nonetheless, studies find much higher incidences of RAS in health care professionals who often are subject to substantial amounts of work-related stress.

One study looked at the incidence of RAS in students in the health care field. Of 485 students, 36.9% had RAS with 8.9% having a current outbreak. Stress correlated with the occurrence of RAS.¹³ Medical students doing internships had the highest incidence of RAS (44%–45.9%), while students at schools of nursing and midwifery and paramedical training had a lower incidence. These results were attributed to that increased stress and inadequate sleep that interns were subject to.¹³ Other studies have reached similar conclusions. Overall, medical and dental students, as a rule, show significantly higher incidences of RAS, compared with the general population (31%–66%).^{11,14}

*The study cited here was reviewed by Casiglia JM, Mirowski GW, Nebesio CL. Aphthous Stomatitis. Emedicine J. Online document at: <http://emedicine.medscape.com/article/1075570-overview> Accessed February 2, 2010.

Adaptogens

Given that RAS may often be triggered by stress, we recommend using adaptogens as an important component of preventing recurrences. Adaptogenic herbs are used to strengthen the body's immune response and increase the individual's ability to cope with physical and mental stress. These agents are also used to increase overall vitality. Adaptogens are generally not used to treat specific ailments but are rather used fairly long-term to help a patient achieve a more healthful state.

Unfortunately, few studies have tested the traditional uses of adaptogens. Most of the research focuses instead on isolated properties of these herbs, such as investigating their hypoglycemic, antimicrobial, or specific immune-system-enhancing effects. There are some clinical studies, but much of the research is published in Asian and Slavic languages, preventing a thorough analysis of the study results in the Western world. As a result, there is surprisingly little solid information on adaptogens despite these herbs' long history of use.

One idea is that adaptogens act by normalizing a patient's nonspecific stress response through the hypothalamic–pituitary–adrenal axis. This axis increases cortisol when animals and humans are subjected to stress, via a reduced sensitivity to feedback downregulation and a disruption in the circadian rhythm of cortisol secretion.

Rhodiola

Rhodiola rosea (rhodiola) is an adaptogen that is the subject of an exhaustive and interesting review.¹⁵ The fragrant root of rhodiola is used in mainstream Russian medicine for fatigue, infectious illnesses, and psychiatric and neurologic conditions. In healthy individuals, this herb is used to relieve fatigue and improve concentration, memory, and productivity. In smaller doses, rhodiola had a stimulating effect on laboratory animals; in larger doses, it had more sedative effects. Its dual action of cognitive stimulation and emotional calming enhances learning and memory while delivering beneficial antioxidant effects to the brain.

In an open study of 53 healthy people and 412 patients with a variety of neurosis and debilities (such as recovering from illness and infection), rhodiola reduced symptoms of fatigue, insomnia, irritability, weakness, and headaches.¹⁶⁻¹⁸ In another open study, 21 physicians and doctors took rhodiola before embarking on intense intellectual work. In all cases, the amount and quality of work performed by these medical professionals increased and their fatigue diminished.¹⁹

At a relatively high dose (300 mg/day), rhodiola improved the accuracy of proofreaders although it did not increase the number of errors caught.²⁰ A lower dose (170 mg/day), improved the functioning of 56 physicians on prolonged night duty during a 2-week period but was not as effective during the last 2 weeks of a 6-week duty period.²¹

In a double-blinded 20-day study of 60 medical students studying for final exams, well-being, physical fitness, mental fatigue, and final-examination grades were improved by the subjects taking a relatively low dose of rhodiola.²² In another double-blinded study, rhodiola increased general well-being while decreasing psychologic fatigue and situational anxiety in high-school students.²³

In a 12-week study, rhodiola, along with vitamins and minerals, reduced exhaustion, forgetfulness, daytime sleepiness, irritability, and other similar complaints. Greater improvements were found in subjects who took a full dose of rhodiola in the morning rather than taking a divided dose over the day. This study was not placebo-controlled.²⁴ In a 6-week study of 79 patients with mild-to-moderate depression, the patients' depression, insomnia, emotional stability but not self-esteem improved significantly with rhodiola, compared with placebo.²⁵ A small study found that rhodiola reduced levels of C-reactive protein and creatine kinase in healthy untrained volunteers after exhaustive exercise.²⁶

Animal and in vitro studies show that rhodiola, like most of the adaptogens, has antioxidant, cardioprotective, anticarcinogenic, and strengthening effects. Rhodiola has a very low level of toxicity with an LD₅₀ in rats equating to a dose of 235,000 mg in an average-sized man. As a typical dose is less than 600 mg/day, there is a large margin of safety.

In our opinion, rhodiola is an excellent choice for individuals bogged down by the stress and fatigue that can be caused by demanding intellectual work—in individuals who tend to have a higher incidence of RAS. It is a good choice for individuals who have trouble concentrating while awake and trouble sleeping at night. We also favor the use of rhodiola in adults because the root is high in tannins, which have been shown to help heal acute canker sores. (See section on tannin-containing herbs, below) We typically recommend rhodiola capsules on a long-term basis, adding rhodiola tea during acute outbreaks to enhance healing through the topical action of the plant's tannins. Now that organic rhodiola is being grown on a larger scale in Alberta, Canada, it is also a more ecologic choice than formerly, when most of the supply was shipped in from Asia.



Glycyrrhiza glabra (licorice).

Licorice

Glycyrrhiza spp. (licorice) is often neglected in discussions of adaptogens, most likely because it can, in excessive doses, act as an aldosterone agonist that raises blood pressure (BP)—a problem in Western culture where high BP is rampant. Nonetheless, licorice is an excellent adaptogen in appropriate cases and is one of the best adaptogens for children. Licorice works well in children, because they are not prone to high BP and usually like the taste of the herb, increasing the ease of achieving compliance with the prescription.

In ancient China, licorice was a primary herb and remains the most commonly used in traditional combination formulas. One Chinese text reports that licorice strengthens sinews and bones, enhances muscle growth, and topically helps heal wounds¹⁹—all useful attributes for treating children, especially those who have RAS. Herbalists favor licorice when they need an herb that is an adaptogen, an immune-modulator, and an inflammation-modulator.¹⁹

Licorice is an immune-modulator, an aspect that supports its use in RAS. The pathogenesis of RAS involves a cell-mediated immune response in which tumor necrosis factor α (TNF α) plays a major role, and RAS can be prevented by drugs, such as thalidomide and pentoxifylline, that prevent the synthesis of TNF α .¹⁰

Other proinflammatory cytokines, such as interleukin-2 (IL-2) and IL-6 also play a role in RAS.^{10,27} Interestingly, smoking and other uses of nicotine help prevent RAS, a fact attributed to a change in production of these inflammatory compounds.¹ Numerous compounds in licorice appear to moderate these chemicals. Thus, one study found that licochalcone A, isolated from *Glycyrrhiza inflata* (another form of licorice) inhibited TNF α strongly.²⁸ Another study showed that licorice flavonoids inhibit expression of inflammatory cytokines in mice with lung inflammation.²⁹ Glycyrrhizin, the

*Echinacea* spp. (echinacea).*Alchemilla vulgaris* (lady's mantle).*Myrtus communis* (myrtle).

main active compound in licorice, blocked induction of proinflammatory mediators and attenuated inflammatory responses in macrophages.³⁰

There are only a couple of studies on using licorice to treat RAS. One study of 15 patients with RAS compared tragacanth-based hydrogel patches with and without licorice over three RAS episodes. The licorice patch provided better pain relief than no treatment but was almost equal to the pain relief provided by the hydrogel without licorice. However, in the patients who had the patches with licorice, the diameter of the ulcer inflammation zone was significantly reduced by day 5, which was attributed to the herb's inflammation-modulating action.³¹

Twenty patients with aphthous ulcers used deglycyrrhizinated form of licorice (DGL) as a mouthwash and gargle (200 mg of DGL dissolved in 200 mL of warm water daily). Fifteen patients reported 50%–75% pain relief in 24 hours and, by day 3, had complete healing of the ulcers. One patient had RAS of 10–12 years' duration without a remission-free period in the previous year. By day 3, 75% of his ulcers had healed; by day 7 he was symptom-free and remained so at a 1-year evaluation. Four patients dropped out of the study, 2 of whom did so because their symptoms were not reduced.³² Of course, licorice, as well as DGL, each have a fairly well-established reputation for helping prevent and heal gastric ulcers, which indicates a probability of usefulness for treating aphthous ulcers.³³

Herbs for Acute Outbreaks

Berberine-Containing Herbs

Historically, berberine-containing herbs have been praised as being highly useful for acute RAS outbreaks. *Coptis* spp. (goldthread) is one of those herbs, and its rootlets have a long history of use for mouth sores. The Eclectics reported back in the late 1800s that goldthread was no longer widely used and also noted that berberine was considered its main constituent.³⁴ However, goldthread remained in use as a wash or gargle for patients with ulcerations of the mouth, for which the herb was deemed “decidedly efficient.”

The Eclectics also reported that for “sore mouth of nursing mothers,” goldthread “repeatedly and promptly cured” cases for which *Hydrastis canadensis* (goldenseal) root had no effect. From this, these physicians concluded that some other compound in addition to berberine was responsible for goldthread's ability to heal these types of mouth ulcers.³⁴

Recently, scientists reached a similar conclusion while looking at a related plant's ability to heal gastric ulcers in rats. An extract of total alkaloids from *Coptis chinensis* was compared to an extract with an equal content of berberine. The total alkaloids had stronger antiulcerative properties than isolated berberine.³⁵

For treating aphthous ulcers, goldenseal was surpassed only by goldthread and *Phytolacca americana* (poke root[†]). Poke root was considered especially effective for treating ulcers described as being “more subacute ulcers bordering on a chronic problem,” which appears to be a description of the recurrent phase of RAS.³⁴

Unfortunately, despite their long history of use for treating RAS, we were unable to find research on the benefit of these berberine-containing herbs or on isolated alkaloids from these plants for treating aphthous ulcers. The berberine-containing herbs are bitter and have the advantage of often improving digestion, which can be an issue for patients who have RAS. Thus, we find these herbs very useful remedies for acute ulcerations in adults. They are—because of their bitter taste—much more difficult to use in children, in whom we favor licorice as discussed above.

Tannin-Containing Herbs

Historically, tannin-rich herbs were often chosen to heal ulcers generally, and such herbs are also often recommended for treating aphthous ulcers. A common home remedy is simply to place a tea bag on the ulcers and let the tannins in the tea

[†]Poke root is a low-dose herb seldom used these days for canker sores despite the high praise the Eclectic physicians accorded the plant. It was once widely used for all types of mouth sores in children and adults where the mucous membranes showed whitish erosions or a “white glaze” over mouth surfaces.

assist in the healing. Certainly, plant tannins have been shown to prevent dermal degradation and enhance wound-healing.³⁶ Of course, most plants used for wound healing have other attributes as well, such as enhancing regranulation of the skin, that make them more useful than a tannin alone would be. Nonetheless, one reason for our recommendation of rhodiola in aphthous stomatitis is that it is a plant rich in tannins.

Three studies have looked at tannin-rich herbs for treating RAS. The first is a Brazilian study reporting that RAS affects close to 50% of the Brazilian population. In this study, a traditional botanical remedy from South America, *Eupatorium laevigatum* (eupatorium; now frequently called *Chromolaena laevigata*) paste was tested for safety in 20 volunteers, and no adverse effects were noted. Subsequently, the paste was tested in a randomized double-blinded comparison with triamcinolone 0.1% in 60 patients. In this study, ulcers healed in 5 days in 40% of patients who were given the paste and in 26.7% of those using triamcinolone. Pain relief was much higher in subjects who were given the herb paste (70% versus 33.3%). The researchers attributed the healing action of the eupatorium paste to tannins in the plant and its anti-inflammatory action to an inhibition of cyclooxygenase (COX)-1 or -2 inhibition, suggesting that the herb's analgesic action was similar to that of nonsteroidal anti-inflammatory drugs (NSAIDs).

The second study looked at the topical use of *Alchemilla vulgaris* (lady's mantle) herb in a glycerine base. In a test group, application of the gel three times daily produced complete healing of ulcers in 60.4% of the patients in 2 days and in 75% of the patients in 3 days, compared with 10.4%/33.3% of the patients in a nontreated group, and 15%/40% in 48 patients. It appears that the data on the healing times of nontreated or other-treated patients were based on responses to a questionnaire.³⁷

Myrtus communis (myrtle) leaf is an astringent herbal medicine used in European traditional medicine. An aqueous extract of the leaves was incorporated into a paste to a final concentration of 5% and compared with placebo in a double-blinded, randomized trial involving 45 Iranian adults with RAS. After treating an episode of acute aphthae, each subject was crossed over to the other treatment for the next acute episode of RAS. While subjects were using the topical myrtle paste (applied four times daily), there were significant reductions in pain and ulcer size, compared with placebo. No attempt was made to determine if the treatment reduced frequency of RAS episodes.³⁸

Spilanthes

One of our favorite herbs for treating aphthous ulcers is *Spilanthes acmella* (spilanthes; also known as *Acemella oleracea*) flowers. This is a South American plant that has been the subject of very little research and none of what was done pertained to RAS. The herb was not widely used by the Eclectics, but they did note that it was useful for treating "inflammations of the mouth."³⁴ One of the herb's common names is "tooth ache plant," as numbing powders made from the herb were often used to quiet the pain of tooth decay. Spilanthes has been used for treating stomatitis in traditional medicine systems in other parts of the world.³⁹



Spilanthes acmella (spilanthes). Drawing © 2010 by Kathy Abascal, B.S., J.D., R.H. (AHG).

Preliminary studies have shown that the plant produces significant anti-inflammatory action against both acute and chronic inflammation as well as producing central and peripheral analgesic activity in animal models.⁴⁰ One animal study found the herb's analgesic effect comparable to aspirin (100 mg/kg/p.o.) and paracetamol.³⁹ Another study found that an aqueous extract of the flowers was antihistaminic and inhibited prostaglandin (PG) synthesis in rats, providing relief from persistent pain.⁴¹

The advantage spilanthes confers is that it appears to speed wound healing while providing substantial pain relief, which is the key component (at least from the patient's point of view) in treating acute ulcers. In fact, the numbing effect is so fast and strong that most patients do well by applying the undiluted tincture directly on their ulcers—although, of course, a tea will provide the same relief without the potential for stinging. Given the similarity in chemical makeup, and its well-known topical anesthetic effect, *Echinacea* spp. (purple coneflower) may be substituted for spilanthes.

Conclusion

Alternative treatments for RAS have a reputation of working effectively although they are not yet well-studied. The most effective treatments should combine taking account of dietary sensitivities, using an appropriate adaptogen, and using at least one of the herbs with a history of use for helping heal acute outbreaks. ■

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