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Botanical Medicine for Cystitis

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Abstract

Plant medicines are used on a worldwide scale to prevent and treat cystitis. Some of the specific medicinal herbs used for cystitis have been investigated by scientific means while others are prescribed on the basis of long histories of safety and efficacy. This article reviews the qualities and research on the most important botanical medicines used in treating cystitis: *Vaccinium macrocarpon* and *V. oxycoccos* (cranberry); *Arctostaphylos uva-ursi* (uva ursi) leaf; *Tropaeolum major* (nasturtium) leaf; *Armoracia rusticana* (horseradish) root; *Agathosma* (formerly *Barosma*) *betulina* (buchu) leaf; *Hydrastis canadensis* (goldenseal) root; *Mahonia aquifolium* (Oregon grape) root; *Berberis vulgaris* (barberry) root; *Coptis* spp. (gold thread); *Solidago* spp. (goldenrod) herb; *Levisticum officinale* (lovage) root; *Betula* spp. (birch) bark; *Taraxacum officinalis* (dandelion) leaf; *Zea mays* (corn) silk; *Agropyron repens* (couch grass) rhizome; *Apium graveolens* (celery) seed; *Juniperus communis* (juniper) leaf; *Crataegus* spp. (hawthorn) berries; *Fragaria* spp. (strawberry) leaves; *Matricaria recutita* (chamomile) flowers; *Equisetum* spp. (horsetail); *Althaea officinalis* (marshmallow) leaf and root; *Ulmus rubra* (slippery elm) bark; *Sphaeralcea* spp. (globemallow) leaf; *Alcea rosea* (hollyhock) leaf and root; *Populus tremuloides* (quaking aspen) bark; *Glycyrrhiza* spp. (licorice) root; *Chimaphila umbellata* (pipsissewa) leaf; *Piper methysticum* (kava) root; and *Scutellaria* spp. (skullcap) herb and root.

Introduction

Plant medicines are used around the world to prevent and treat cystitis. Some of the specific medicinal herbs used for this purpose have been investigated by scientific means, while others are known to be effective and safe on the basis of a long history of use. This article discusses general information about infectious and interstitial cystitis (IC), and explores the qualities of the most important botanical medicines used to treat these conditions.

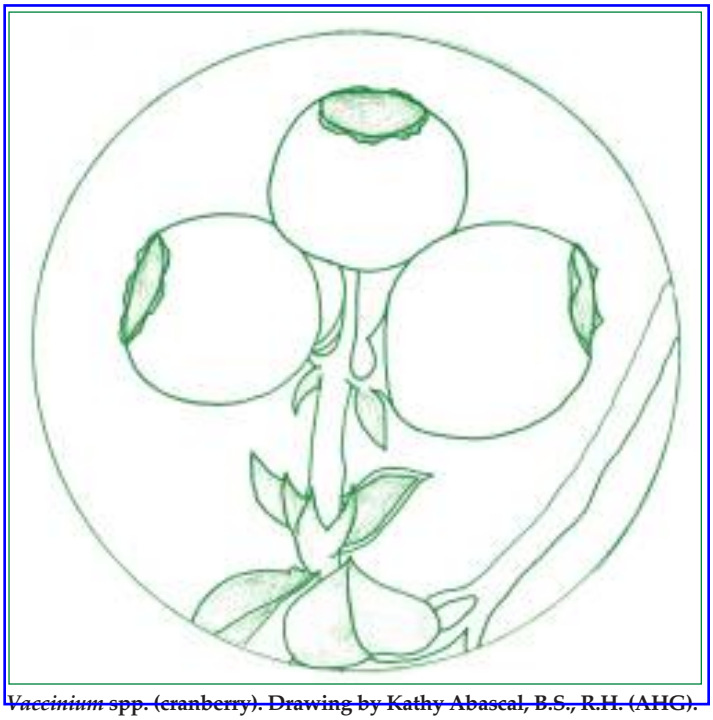
Infectious Cystitis

Bacterial infections of the urinary bladder continue to plague women in particular, although uncircumcised boys have a slightly increased risk of such infections. Enteric pathogens, particularly *Escherichia coli*, cause almost all cases of bacterial cystitis. These pathogens express a number of molecules that allow them to adhere to different cell types on their journey from the bowel to the bladder, and such bacterial adhesion probably constitutes the first step toward establishing a urinary tract infection (UTI).[1]

In the case of most strains of *E. coli* and other cystitis-causing Enterobacteriaceae, binding occurs through the linkage of bacterial Type 1 fimbriae to mannose residues on host mucous or cell membranes. The fimbriae play a crucial role in bacterial adhesion to cells of the perineum, vagina, and foreskin.[2] However, type 1 fimbriae do not appear to play an important role once the bacteria are established in the urinary bladder; rather, research implicates P fimbriae and afimbrial adhesin molecules as the main culprits in allowing gut bacteria to cling to bladder epithelial surfaces.[1] Adherent bacteria can then initiate the steps that lead to bladder inflammation and clinical symptoms. Fimbriae, particularly P fimbriae, also play an important role in the progression of cystitis to pyelonephritis.[3] As subsequently discussed, there are botanical remedies that can interfere with this critical step in the pathogenesis of UTI.

Many antibiotics, including trimethoprim-sulfamethoxazole (TMP-SX) commonly used to treat UTIs, exert a weak to nonexistent effect on bacteria that have adhered to the bladder epithelium.[4] Although antibiotics are often effective in relieving symptoms of acute cystitis, these drugs may not be very effective at eliminating colonization, and may also adversely affect the vaginal and urethral flora, facilitating the establishment of uropathogens.[5] A vicious cycle can ensue when antibiotics used to treat UTIs cause gut, vaginal, or periurethral dysbiosis and thereby set the stage for new or recurrent UTIs.[6] Antibiotics also induce a high level of antibiotic resistance among bladder bacteria, arguing for greater caution in their use.[4,7] Probiotic supplementation is recommended during and after antibiotic use of any kind, to prevent or correct dysbiosis induced by these drugs.[8]

Other host factors contributing to the pathogenesis of lower UTIs depend on age. In children, congenital anomalies of the urinary tract and vesicoureteral reflux contribute to many instances of cystitis. Sexual abuse may also occasionally be a factor in UTIs during childhood. In adults, inadequate urine output secondary to insufficient water intake, various sexual practices (particularly those involving the anus), and spermicide use are all risk factors for lower UTIs. Spermicides, especially nonoxynol-9, appear to disrupt the normal vaginal flora and normal vaginal pH, thereby removing



Vaccinium spp. (cranberry). Drawing by Kathy Abascal, B.S., R.H. (AHG).

two of the normal female defenses against bacterial colonization of the bladder.[9] Among the elderly, urolithiasis, prostatic obstruction of urinary outflow, and confinement to bed may be involved in UTIs. Frequent or recurrent catheterization strongly predisposes patients to infectious cystitis. Patients with P1, an erythrocyte surface marker not usually measured clinically, are also at greater risk of colonization, in that this produces receptors to which bacterial fimbriae adhere avidly.

Cranberry

Cranberry (*Vaccinium macrocarpon* and *V. oxycoccos*) is a member of the heath (Ericaceae) family and grows in bogs in the northeastern United States and eastern Canada. European colonists adopted it from the indigenous peoples of North America. Besides the use of cranberry as a food, it was also applied to treat urolithiasis and several other conditions, and cranberry juice historically found use as a folk remedy for UTIs.

Initial clinical reports suggested that cranberry was effective either because it acidified the urine or through the plant's content of benzoic acid, which is converted to hippuric acid in the urine and which may be antimicrobial.[10,11] However, it would be necessary to drink at least 1500 mL of cranberry juice a day to consistently maintain the urinary pH of 5.5 that is associated with an antibacterial effect.[12] For most people this volume of cranberry juice is simply too great to consume on a daily basis.

The mechanism by which cranberry exerts an antibacterial effect has been elaborated in the past 20 years. Cranberry appears to interrupt the binding of bacterial type 1 and P fimbriae in both the urinary bladder and the gut.[13] The effect is to block microbial adhesion rather than to kill microbes directly, although there is some evidence that cranberry also has mild, direct antimicrobial activity.[14] However, if bacteria cannot adhere to the urothelium of the bladder, there is no reason to kill them, since they will be removed with the urine and be unable to initiate infection. This also avoids disruption of the normal urinary flora.

Summary of Major Botanicals Used for Cystitis

Botanical name	Common name	Main Constituent(s)	Main action in urinary tract
Agathosma betulina	Buchu	Terpenoids, mucilage, flavonoids	Antibacterial
Agropyron repens	Couchgrass	Mucilage, terpenoids, glycosides	Soothing, possibly prevents bacterial adhesion
Althea officinalis	Marshmallow	Mucilage	Soothing
Apium graveolens	Celery	Terpenoids	Aquaretic, Inflammation modulating
Arctostaphylos uva-ursi	Uva ursi	Arbutin	Antibacterial
Betula spp.	Birch	Salicylates, terpenoids	Aquaretic, inflammation modulating
Chimaphila umbellata	Pipsissewa	Arbutin	Antibacterial
Equisetum arvense	Horsetail	Saponins, alkaloids	Aquaretic
Glycyrrhiza glabra	Licorice	Glycyrrhizin, flavonoids	Inflammation modulating, soothing
Hydrastis canadensis	Goldenseal	Berberine, hydrastine, and related alkaloids	Antibacterial, immunostimulant
Juniperus communis	Juniper	Terpenoids	Aquaretic, antimicrobial, inflammation modulating
Levisticum officinale	Lovage	Coumarins	Aquaretic
Piper methysticum	Kava	Kava lactones, resin	Sedative
Populus tremuloides	White poplar	Glycosides	Inflammation modulating
Scutellaria spp.	Skullcap	Flavonoids	Sedative
Solidago virgaurea	Goldenrod	Flavonoids, glycosides, saponins	Aquaretic, inflammation modulating
Taraxacum officinalis	Dandelion	Glycosides, terpene lactones	Aquaretic
Vaccinium macrocarpon	Cranberry	Proanthocyanidins	Prevents bacterial adhesion
Zea mays	Corn silk	Mannose, mucilage	Aquaretic, possibly prevents bacterial adhesion

In laboratory experiments, cranberry prevented adhesion of uropathogens (*Proteus* spp., *Pseudomonas* spp., and *E. coli*) to bladder epithelial cells.[15,16] The major antiadhesive constituents of cranberry have been identified as proanthocyanidins.[17,18] These protective substances are not present in most other fruits, including guava, mango, orange, grapefruit, or pineapple,[19] although they are present in the cranberry-related blueberry or bilberry (*Vaccinium myrtillus*).

In a large, double-blind study, 153 women with a mean age of 78 years, who had bacteriuria and pyuria, were given 300 mL of saccharin-sweetened cranberry juice daily or a placebo juice.[20] Significantly more women drinking cranberry juice developed sterile urine than did those taking the placebo juice. This study did not show a protective effect of cranberry against new bacterial colonization, but only a conversion from colonized to noncolonized status. However, reduction or elimination of bacteria, which cranberry juice achieved to a clinically relevant degree, is an important step toward preventing frank cystitis. In another, smaller study involving 12 women who had had at least 6 UTIs in the preceding year, none of the women taking 400 mg of cranberry extract daily for 12 weeks experienced a UTI. Eight (8) of the women continued taking the extract after the study ended, and 2 years later, none had experienced an infection.[21] A systematic review found that the prophylactic use of cranberry in individuals with recurrent UTIs significantly reduced the incidence of such infections at 12 months.[22]

Cranberry juice has also been found to reduce odor and to yield clearer urine in children required to regularly catheterize themselves,[23] and has proven useful in reducing catheter-obstructing mucus production in patients with entero-urocystoplasties.[23,24] Additionally, an open trial found find that 250 mL of cranberry juice taken three times daily reduced bacterial biofilms in patients with spinal-cord injuries affecting bladder function.[24] However, a double-blind trial involving children with neurogenic bladders and requiring intermittent catheterization failed to find that cranberry concentrate reduced bacteriuria to a greater extent than did an artificially flavored cranberry drink.[25] In a randomized double-blind trial of 305 patients with neurogenic bladders following spinal cord injury, an 800-mg cranberry capsule taken twice daily failed to prevent UTI.[26]

The relationship between cranberry and kidney stones is often discussed, though there is little solid information to suggest that it has either a beneficial or a detrimental effect. Sufficient intake of cranberry to chronically acidify the urine may help prevent some types of urinary stones (struvite and calcium phosphate) from forming, but again, the volume required is impractical for most people. Moreover by far the most common type of uroliths in the developed world, calcium oxalate stones, tend to occur in acidic urine, suggesting that high-dose intake of cranberry would actually promote stone formation. A study comparing 12 healthy individuals with 12 patients having a tendency to calcium oxalate stone formation found that 1 liter of cranberry juice per day had a mixed effect on stone formation, but increased the overall risk of calcium oxalate and uric acid stone formation while decreasing the risk of brushite stones.[27] Another human trial found that cranberry tablets increased urinary oxalate levels in 5 healthy volunteers, leading the authors to conclude that "[p]hysicians and manufacturers of cranberry products should make an effort to educate patients at risk for nephrolithiasis against ingestion of these dietary supplements."[28] However, these latter authors' own study contradicts their conclusion, for they found that urine levels of magnesium and potassium rose with cranberry intake, an effect that is associated with a reduction in the risk of kidney stones. Overall, their findings were based only on indirect measures that do not necessarily equate to stone formation, and were based on a very small sample size. To make such a sweeping statement against use of cranberry based on such weak data is irrational. Unbiased research is needed on the effect of cranberry on the risk of urolithiasis. In the meantime, blanket statements for or against cranberry based on the existing, highly incomplete data should be condemned.

***Vaccinium* spp. (cranberry).**

Although cranberry in therapeutic doses has no known toxicity and is safe for use by pregnant women, it may cause mild gastrointestinal (GI) upset in a few people. Sweetening of the juice should be avoided or minimized. Cranberry in therapeutic doses does not decrease the effectiveness of *Arctostaphylos uva-ursi* (uva ursi) or antibiotics because cranberry rarely acidifies the urine enough to interfere with uva ursi's action (see discussion below). Capsules providing at least 400 mg of cranberry extract prevent problems for patients with blood-sugar imbalances who need to avoid sweetened juice yet dislike the taste of unsweetened cranberry. The capsules can be used in a dosage of 2 or 3 capsules per day (higher doses may be needed for acute UTIs). Overall, cranberry is an excellent agent for preventing the adhesion of uropathogens in most patients with UTIs or related conditions.

***Berberis vulgaris* (barberry).**

***Tropaeolum major* (nasturtium).**

Other Botanicals

A variety of botanicals other than cranberry can prevent and treat cystitis. Although many have not been investigated systematically with modern methods, the long history of their use strongly indicates that they should be examined in controlled clinical studies. The three main categories of herbs used medicinally for the urinary tract are urinary antiseptics, diuretics (technically aquaretics, as will be explained), and demulcents. The following sections cover only those in wide use.

Urinary Antiseptics

Some urinary antimicrobial botanicals commonly used in North America are uva ursi leaf, *Agathosma* (formerly *Barosma*) *betulina* (buchu) leaf, *Tropaeolum major* (nasturtium) leaf, *Armoracia rusticana* (horseradish) root, and berberine-containing herbs, including *Hydrastis canadensis* (goldenseal) root, *Mahonia aquifolium* (Oregon grape) root, *Berberis vulgaris* (barberry) root, and various species of *Coptis* (gold thread).

The first of these, uva ursi (also known as bearberry or kinnikinnick), is native to North America, where it grows as a low shrub. Its leaves contain relatively high levels of the phenolic glycoside arbutoside (also known as arbutin). Most arbutin is absorbed directly via glucose transporters, and then hydrolyzed in the liver to aglycone (known as hydroquinone) and glucose.[29] Some hydroquinone is absorbed from the gut. The hydroquinone is conjugated in the liver to glucuronic acid and sulfides, making it water-soluble. Hydroquinone glucuronide and hydroquinone sulfide are then excreted into the urine. In alkaline urine (pH 8 and above[30]), the complex dissociates spontaneously, releasing free hydroquinone, which has antimicrobial activity.[31] However, a study of 3 people has suggested that the recommended dose of uva ursi of 3 g in 150 mL of water, administered 4 times per day—which is the equivalent of 400–840 mg of arbutin per day—results only in minimal excretion of free hydroquinone.[32] This strongly suggests that hydroquinone glucuronide and sulfide also contribute to the antimicrobial activity of the herb. Maximum urinary antiseptic activity of uva ursi occurs 3–4 hours after its oral ingestion. A high intake of fruits and vegetables will sufficiently alkalinize the urine for efficacy of uva ursi in some people; others may have to take 6–8 g of sodium bicarbonate daily for this, although this will also reduce stomach acidity, which is usually an undesirable action.

The alkalinity required to produce the antimicrobial hydroquinone from uva ursi has raised concern that it not be combined with cranberry, since the latter can supposedly acidify the urine at to an extent that renders this hydroquinone ineffective. However, it is now known that a volume of cranberry of more than 1500 mL/day is probably needed for such urinary acidification, indicating that most people can safely use uva ursi together with cranberry.

A double-blind trial of 1 month's use of an uva ursi extract standardized to arbutin and methylarbutin in women with recurrent cystitis, defined as 3 or more infections in the previous year, found that uva ursi stopped further episodes of cystitis in the year following the study.[33] In contrast, 23% of women in a placebo group in the study experienced at least 1 further episode of cystitis in the year after conclusion of the study. The difference between the groups was both statistically and clinically significant.

Uva ursi also contains tannins, which can cause nausea. Two methods of avoiding this are for patients to take uva ursi with meals or to make a cold infusion of the herb, into which the tannins are poorly extracted. A typical regimen of uva ursi involves adding 4–5 tbsp of the leaves of the herb to 1 quart of water and allowing this preparation to steep overnight. The preparation

should then be strained and the fluid consumed in divided doses throughout the next day. Larger quantities can be made ahead of time but should be kept in the refrigerator since they will otherwise rapidly decompose.

The hydroquinone generated from uva ursi has a number of potentially dangerous effects including suppression of B lymphocyte maturation and nephrotoxicity.[34,35] Hydroquinone is also a known mutagen, and is one of the many toxins in cigarette smoke that contribute to cancer. This suggests that uva ursi should not be used over the long term, though the absolute levels of free hydroquinone that it generates in the urine are exceedingly small (or entirely absent according to one pharmacokinetic study in humans[36]). At least one double-blind trial has shown no short-term adverse effects of continuous use of uva ursi for up to 1 month.[32]

Among other herbal products for UTI, a German clinical trial found a combination of horseradish root extract and nasturtium leaf to be just as effective as antibiotics, and significantly safer than the latter, in curing uncomplicated UTIs.[37] In a double-blind follow-up trial involving 219 adults, the rate of UTI was roughly halved with this same herbal extract as compared to placebo.[38] No difference in adverse effects was seen in the herb and placebo groups. Both horseradish root and nasturtium are traditionally also used for infections in other parts of the body than the urinary tract.

Buchu leaves, obtained from the South African plant *Agathosma betulinum* and several related species, contain various terpenes, flavonoids, and other substances. The plant has a long history of use as an antiseptic in UTI,[39] and is also used in gout, rheumatism, and mild GI upsets. Because its efficacy has not been confirmed in any clinical trial, this herb should probably be regarded as a second-line treatment for UTI, behind other herbs with known efficacy. It is also generally better, both economically and ecologically, to avoid using herbs from outside North America if there are acceptable local alternatives.

Herbs containing berberine are used for treating many types of infection throughout the body. This alkaloid is clearly antimicrobial in sufficiently high concentrations, and like cranberry may also be important as a microbial antiadhesive agent. Berberine has been shown to decrease the expression of fimbriae by *E. coli*, hence preventing their adhesion to the bladder epithelium.[40] Berberine also blocks adhesion to the urothelium of *Streptococcus pyogenes* at concentrations insufficient to inhibit growth, and interferes with the lipoteichoic acid complexes that allow streptococcal adhesion to fibronectin.[41]

Berberine has proven useful and well tolerated as a treatment for enterotoxigenic *E. coli* infections,[42] and has been shown *in vitro* to inhibit adhesion of uropathogenic strains of *E. coli*.[40] However, while herbs containing berberine have been used empirically with success, they yield only minute urinary levels of this alkaloid when administered orally in humans,[43] raising doubt that they would influence UTIs, and no clinical trials have examined whether administration of berberine-containing plants can prevent or alter the course of cystitis.

Standardized extracts usually contain 5%–10% berberine. Historically, treatment of UTI with berberine has consisted of 1 tsp (5 mL) of a tincture of any of the berberine-containing plants named above, taken three times daily. Alternatively, a 250–500 mg capsule containing the ground root of berberine-containing plants can be taken three times daily.

***Taraxacum officinalis* (dandelion).**

Goldenseal, Oregon grape, barberry, and gold thread are the major medicinal herbs containing berberine, and all are very safe. All are digestive bitters, which means that they stimulate the entire digestive tract and may in some instances cause nausea. As a result, they should be used with caution if at all in conditions of hyperchlorhydria with increased gut motility especially as evidenced in the form of diarrhea. However, berberine-containing plants are indicated in conditions of infectious diarrhea.

There is also some preclinical evidence that berberine displaces bilirubin from albumin, suggesting that berberine should be avoided in late pregnancy.[44]

Aquaretic Herbs

According the late pharmacognocist Varro E. Tyler, Ph.D. (1926–2001), most botanicals used for UTIs and other conditions are not technically diuretics but aquaretics.[45] This means that plants traditionally referred to as diuretics may not act by interfering with the renal handling of ions, but instead may act to increase blood flow to the kidneys and thereby raise the glomerular filtration rate. Whether they are aquaretics or diuretics, these agents can benefit patients with UTIs, in which increased urine flow helps wash bacteria out of the urinary bladder.

Some major, traditional phytoaquaretics are *Solidago* spp. (goldenrod) herb, *Levisticum officinale* (lovage) root, *Betula* spp. (birch) bark, *Taraxacum officinalis* (dandelion) leaf, *Zea mays* (corn) silk, *Agropyron repens* (couch grass) rhizome, buchu, *Apium graveolens* (celery) seed, and *Juniperus communis* (juniper) leaf.

Dr. Tyler reviewed research showing goldenrod, buchu, parsley, juniper, and birch to be aquaretic, at least in animals.[44] A double-blind, placebo-controlled trial, conducted in Vietnam, failed to show

Clockwise: *Fragaria* spp. (strawberry) leaf, *Betula* spp. (birch) bark, *Zea mays* (corn silk), and *Crataegus* spp. (hawthorn).

any increase in urine output after intake of corn silk.[46] Dandelion leaves were shown to have a diuretic effect in rats.[47] A recent abstract reported that a combination of birch leaves, hawthorn (*Crataegus* spp.) berries, strawberry (*Fragaria* spp.) leaves, corn silk, *Matricaria recutita* (chamomile) flowers, and horsetail (*Equisetum* spp.) had a 47% greater diuretic effect than horsetail alone and 34% greater effect than a hydrochlorothiazide suspension in rats.[48] This suggests that combining herbs with medicinal foods will often work better than using an herb alone. Celery, parsley, and carrots should be emphasized in the diet because they promote urine flow and generally support the urinary tract. Ultimately, effective treatment of cystitis requires at least 8 glasses a day (part of which is often replaced by unsweetened cranberry juice or herbal teas).

No research has been done on the aquaretic action of couch grass, but in one study it failed to prevent kidney stone formation in rats,[49] and since increased urine flow is known to help prevent kidney stones, couch grass appears not to be a very potent aquaretic. The herb does, however, appear to contain enough mannose to prevent uropathogen adhesion to the bladder mucosa via type 1 fimbriae. Jonathan Wright, M.D., of Kent, Washington, uses 0.25–1 tsp of mannose dissolved in water, given three or four times a day to prevent mucosal adhesion of bacteria in cystitis. The mannose in corn silk may help explain its traditional use in treating cystitis.[50] The efficacy of mannose is, however, still uncertain, since it has not yet been examined in a clinical trial.

The Australian herbalist Nicolas Burgess, (currently affiliated with Phytomedicine Pty. Ltd. and president of the National Herbalists Association of Australia) recommends celery seed as a useful diuretic in UTIs, and also observes that celery seed is rapidly becoming a major remedy for osteoarthritis in Australia. In Britain, celery seed is considered to be only a mild diuretic and is largely recommended for rheumatic conditions and gout.[51] Celery seed should not be used in persons with renal disease because the seed's volatile oils may "irritate" the kidney with prolonged administration. Light-skinned persons may also want to avoid excessive intake of celery seed because of a slight risk that it may induce photosensitivity.

Juniper offers a very appealing herbal "package" for patients with UTIs. Besides its potent diuretic activity, it is strongly antimicrobial and anti-inflammatory.[52,53] It is surprising that all of these properties have not led to a published clinical trial of juniper for UTI. The reputation of juniper as dangerous to the kidneys is of dubious accuracy, and one text that attempted to trace the origin of this belief could find only that it was due to confusion of the essential oil of *Juniperus sabina* (savin) with that of juniper.[54] In a study with rats, high doses of juniper oil produced no nephrotoxicity.[55] However, juniper should be used with caution in pregnancy on the basis of unconfirmed historical reports of its having uterine-stimulating effects.

Demulcent Herbs

There is a significant overlap between the aquaretic botanicals and those said to soothe irritated urothelial surfaces. The latter demulcents include corn silk, couch grass, *Althaea officinalis* (marshmallow) leaf and root, *Ulmus rubra* (slippery elm) bark, *Sphaeralcea* spp. (globemallow) leaf, and *Alcea rosea* (hollyhock) leaf and root. Although all clearly contain significant mucilaginous material, no research has been done on their therapeutic benefit in cystitis; however, all are exceptionally safe.

It is thought that demulcent agents work via a reflex action: As they pass through the digestive tract they are believed to provoke neurologic reflexes that in turn stimulate production of mucus in the respiratory and urinary tracts. This has not been confirmed in the urinary tract, though it has been shown to occur in the respiratory tract in animals.[56] This increased mucus production is thought to relieve inflammation and soothe pain. Whatever the mechanism of their effect, it is clear that in clinical practice demulcent herbs help relieve symptoms of irritation.

Demulcents are usually used in the form of cold infusions. A typical dose is prepared from 1 tbsp of herb per cup of water (often an entire day's dose is prepared at once), with at least 3 cups consumed per day, although higher doses may be needed to alleviate acute symptoms.

Interstitial Cystitis

While interstitial cystitis (IC) was first described about 100 years ago, little has been elucidated about its etiology or pathogenesis.[57] It affects middle-age white women almost exclusively.

Clinically, its most common symptoms are urinary frequency and urgency, pelvic pain or pressure, and burning on urination.[58]

A number of theories have been advanced for the pathogenesis of IC, with significant but imperfect evidence supporting each major theory.[59] Although Hunner initially described ulcerations of the bladder in most affected patients, it is now known that approximately 80% of patients with IC lack such ulcers. In many patients mast cells infiltrate the bladder wall, although their exact role in the disease is still unclear. High levels of histamine and methylhistamine are found in the urine of IC patients as compared to controls,[60] suggesting that mast cell degranulation may contribute to the inflammatory process in the bladder in IC. Other inflammatory mediators derived from bladder epithelial cells, such as interleukin-6, have also been found in the urine in IC.[61]

The glycosaminoglycan (GAG)-rich bladder epithelium may be disrupted in patients with IC, allowing toxic substances in the urine to damage the bladder wall.[62–64] This has prompted a likening of IC to intestinal hyperpermeability. Morphologically, the GAG-rich mucous barrier has a similar appearance in people with IC and those without.[65] However, there may be a difference in the composition, quality, or rate of turnover of the mucus. This was confirmed in a study that found less type IV collagen in the basement membrane of the bladder epithelium of patients with IC.[66] A large clinical trial found that GAG replacement therapy, using sodium pentosanpolysulfate, was no better than placebo for reducing bladder inflammation and symptoms in IC.[67] Direct intravesical application of heparin, a naturally occurring GAG, was successful in a separate study.[68]

The occurrence of IC primarily in women initially raised the idea that the disease might be an autoimmune condition, since women are also the population chiefly affected by most other autoimmune diseases. Studies of this intriguing theory have found an association between Sjögren's syndrome and IC, increased levels of complement component C3 in patients with IC, and a variety of other features resembling those in other autoimmune diseases.[56] Another finding has been that of unique antinuclear antibodies (ANAs) in the sera of patients with IC.[69] An uncontrolled study found that low-dose cyclosporin, an immunosuppressant, was of benefit in IC patients.[70] More clarifying research needs to be conducted in this area, but a case can be made for an autoimmune component in IC.

The role of microbes in the etiology of IC remains uncertain. DNA from gram-negative bacteria can be isolated in as many as 30% of IC patients but not from controls, suggesting that IC may be a form of infectious cystitis.[71] However, the majority of patients with IC have sterile urine.

Natural Interventions for Interstitial Cystitis

Given the complexity of IC, and particularly the variety of pathologic factors it involves, no single "magic bullet" exists for IC treatment. Multiherbal formulae are therefore often utilized for this purpose. Each can address different factors that contribute to IC, and botanical remedies are often combined with other treatment modalities to improve the efficacy of treatment.

Inflammation-modulating botanicals are a component of every formula for treating IC. *Solidago virgaurea* and related species (goldenrod) herb and *Populus tremuloides* (quaking aspen) bark are common choices in this regard. Human studies have confirmed the traditional understanding that goldenrod has aquaretic properties.[72] Animal studies indicate that it also has anti-inflammatory and spasmolytic activities.[73] Although it can provoke allergic reactions in susceptible persons, and should be used cautiously in persons with renal disease, goldenrod is generally safe. Quaking aspen is less thoroughly studied, though both it and birch—both of which contain salicylates—are useful for easing symptoms of cystitis. A typical dose of goldenrod, quaking aspen, or birch tincture is 3–5 mL taken three times daily.

Another good choice as an inflammation-modulating component of herbal formulas for IC is *Glycyrrhiza glabra* (licorice) root, which spares endogenous cortisol by inhibiting 11-beta-hydroxysteroid dehydrogenase type 2 enzyme that converts cortisol and corticosterone to inactive cortisone.[74] Licorice exerts other effects that might benefit patients with IC. For example, it has been shown to reduce complement levels, a known pathogenetic factor in IC.[75] Although the glycyrrhetinic acid in licorice appears to interfere with the inflammatory cascade by acting primarily on the early complement component C2, it may also affect C3, another inflammation-related complement component that appears to be commonly deranged in IC.[56] Anecdotally, licorice is also a demulcent.

Long-term use of high doses of licorice can lead to hypokalemia, hypertension, metabolic acidosis, and other problems.[76] Concomitant supplementation with potassium, consumption of a diet with a high-potassium content (high in fruits and vegetables), and glycine given as a dietary supplement may reduce the risk of such complications. Licorice should not be given to patients taking potassium-wasting diuretic agents, since they increase the toxicity of this herb, and deglycyrrhizinated licorice extracts are unlikely to be effective for IC. A usual dose of licorice fluid extract is 3–5 mL taken three times a day.

Quercetin, the ubiquitous, inflammation-modulating plant flavonoid, was shown in an open trial, to alleviate symptoms of IC.[77] The dose used was a relatively low 500 mg taken twice daily. Quercetin has also proven efficacious in a double-blind trial in patients with chronic prostatitis, a condition closely related to IC and sometimes confused with it.[78] Quercetin-rich foods include green tea, apples, and onions.

Botanical aquaretics are standard features in most formulas for IC. However, this can be highly counterproductive, since a common primary symptom of IC is urinary frequency, obviating the need for further urination. That said, tonic herbs that are mildly aquaretic at most may still have a place in therapy as they are primarily strengthening. A mild aquaretic that is very safe is *Equisetum arvense* (horsetail), but it is unclear whether the active constituents of this herb are extracted in alcohol.

Antimicrobial herbs are included in herbal formulas for IC because part of its pathogenesis may involve bacteria. Uva ursi and sometimes the more soothing arbutin-containing herb *Chimaphila umbellata* (pipsissewa) leaf are used for this. The latter is very mild and almost never causes adverse reactions.

Finally, sedative herbs such as *Piper methysticum* (kava) and *Scutellaria* spp. (skullcap) should also be used in treating IC. Studies show that kava is analgesic via non–opioid-mediated pathways, which might benefit patients who have IC and significant pain.[79–82] Clinical trials show that kava also helps alleviate anxiety.[83] Future studies of kava efficacy in IC are warranted. Kava in therapeutic doses is generally not associated with toxicity; however, its administration should be carefully monitored in patients taking dopamine-antagonist antipsychotic medications or any medications that may adversely affect liver function. A typical dose of kava tincture is 3–5 mL taken three times a day. Extracts standardized to contain 30% kava lactones and containing 70 mg of dried extract per capsule are available. The usual dose is 1 capsule three times daily. Extracts standardized to > 30% kava lactones are not recommended because the lactones may displace other important constituents of kava.

Conclusion

Most patients will benefit most if a multifaceted botanical formula is combined with other therapies. Self-care and behavioral techniques help patients understand and cope with symptoms of IC, as well as reducing their intensity.[84,85] Treatment of IC may also involve direct instillation of dimethylsulfoxide (DMSO) into the bladder by a urologist. Eating a whole-foods diet and avoiding stress are generally recognized as beneficial. □

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