Herbal Support for Methicillin-Resistant *Staphylococcus aureus* Infections

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a modern plague of growing proportions. Herbal medicine offers two potential solutions to this major health issue. First, in some cases, herbs may be substituted for antibiotics altogether. This approach reduces antibiotic use and thus helps prevent worsening of antibiotic resistance, while still controlling the MRSA. Second, herbs can augment the effect of antibiotics and even overcome drug resistance when antibiotics are appropriate and necessary.

This article discusses herbs that potentially have these benefits: The herbs include *Camellia sinensis* (green tea) leaf, *Theobroma cacao* (chocolate) fruit, *Melaleuca alternifolia* (tea tree) leaf essential oil, *Pelargonium sidoides* (African geranium) essential oil, *Cymbopogon flexuosus* (lemongrass) essential oil, *Thymus capitatus* (thyme) flowering top essential oil, *Lavandula* spp. (lavender) essential oil, *Panax ginseng* (Asian ginseng) root, *Panax quinquefolius* (American ginseng) root, *Geranium caespitosum* (pineywoods geranium) herb, *Rosmarinus officinalis* (rosemary) leaf and essential oil, *Lycopus europaeus* (bugle weed) herb, *Santalum spicatum* (Australian sandalwood), *Origanum vulgare* (oregano) herb essential oil, *Allium sativum* (garlic) bulb, *Mahonia aquifolium* (Oregon grape) root, *Hypericum perforatum* (St. John's wort) herb, *Bursera microphylla* (elephant tree) resin, *Commiphora molmol* (myrrh) resin, *Cinnamomum zeylanicum* (true cinnamon) bark volatile oil, *Echinacea angustifolia* (echinacea) root, *Quercus* spp. (oak) bark, *Anemopsis californica* (yerba mansa) root, *Usnea* spp. (old man's beard) thallus, *Juniperus communis* (juniper) fruit, *Larrea tridentata* (chaparral) herb, *Glycyrrhiza glabra* (licorice) root, *Zingiber officinale* (ginger) rhizome, and *Syzygium aromaticum* (clove) volatile oil.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA), a serious infection, is occurring more frequently. Despite the focus on the resistance of this organism to methicillin, the reality is that it is a multidrug-resistant infection. Because of the ongoing, nearly indiscriminate use of broad-spectrum antibiotics and presence of low doses of these antibiotics in animal feed, MRSA and, even worse, antibiotic-resistant infections will continue to be a major problem. The use of ever more potent antibiotics in conventional medicine is causing the emergence of even more drug-resistant MRSA (such as the upcoming plague of vancomycin-resistant *S. aureus*).

Herbal medicine offers two potential ways out of this trap. First, in some cases, herbs may be substituted for antibiotics altogether. This reduces antibiotic use and thus helps prevent worsening of antibiotic resistance while still controlling the MRSA. Second, herbs can be used to augment the effect of antibiotics and even overcome drug resistance, particularly by blocking efflux pumps, when they are absolutely necessary. This article discusses herbs that potentially have these benefits.

The Biology of MRSA

This dangerous strain of organism has attained methicillin resistance and thus carries the MRSA moniker. Methicillin resistance in penicillin-resistant *S. aureus* was documented within 2 years of the introduction of methicillin in 1959.[1] MRSA is unlike many other prior antibiotic-resistant infections in that it occurs more often in the community in people with no exposure to health care institutions.[2] Many studies have confirmed that MRSA infections have higher rates of mortal-

DOI: 10.1089/act.2009.15402 • MARY ANN LIEBERT, INC. • VOL. 15 NO. 4 AUGUST 2009

Proposed Comprehensive Approach to MRSA

For mild or early cutaneous MRSA infections

1. Apply multiple topical antimicrobial herbs, usually essential oils, although creams or ointments are also appropriate, in a base of honey.*,†
   A sample topical volatile oil formula includes:

   - *Melaleuca alternifolia* (tea tree), 25%
   - *Santalum spicatum* (Australian sandalwood), 25%
   - *Origanum vulgare* (oregano), 25%‡
   - *Rosmarinus officinalis* (rosemary), 20%
   - *Pogostemon patchouli* (patchouli), 5% (base/absorption enhancer¶).

   Instruct the patient to apply 3–5 drops over the affected area 2–3 times per day and cover with honey and a bandage. An antibacterial cream formula should include a base cream of *Allium sativum* (garlic), 30 mL. Add the following tinctures to the cream:

   - *Mahonia aquifolium* (Oregon grape) root, 5 mL (antimicrobial)
   - *Hypericum perforatum* (St. John's wort) herb, 5 mL (antimicrobial)
   - *Camellia sinensis* (green tea) leaf, 5 mL (resistance modulator)
   - *Bursera microphylla* (elephant tree) resin, 5 mL (antimicrobial).

   If these herbs are not available, substitute *Commiphora molmol* (myrrh) resin, 5 mL, and *Cinnamomum zeylanicum* (true cinnamon) bark volatile oil, 5 drops (antimicrobial). Instruct the patient to apply the cream liberally over affected area 3–5 times per day and cover with honey and a bandage.
2. Instruct the patient to eat a minimum of 3 fresh cloves of garlic per day.
3. Instruct the patient to take an immune stimulator orally, such as *Echinacea angustifolia* (echinacea) root tincture, 3–5 ml t.i.d. or more often.
4. Instruct the patient to drink plenty of water, avoid all sugar, eat healthy foods lightly, get sunshine (including, if possible, directly on the affected area, being careful not to cause a sunburn), and rest/reduce stress.

For more serious cutaneous MRSA infections

1. Apply topical antimicrobial herbs as stated for milder infections. Consider instructing the patient to apply these more frequently or to use more than one type of application interchangeably.
2. *Quercus* spp. (oak) bark poultice or fomentation applied 2–3 times per day for 30–60 minutes to the wound, between applications of other topical treatments.#,‖
3. Instruct the patient to take a high-dose antimicrobial herbal formula internally. A sample spicy MRSA formula includes:

   - *Anemopsis californica* (yerba mansa) root tincture, 25%
   - *Usnea* spp. (old man's beard) thallus tincture, 20%
   - *Juniperus communis* (juniper) fruit tincture, 15%
   - *Larrea tridentata* (chaparral) herb tincture, 10%
   - Propolis resin tincture, 10%
   - *Glycyrrhiza glabra* (licorice) root fluid extract, 10%**
   - *Zingiber officinale* (ginger) rhizome tincture, 10%
   - *Syzygium aromaticum* (clove) volatile oil, 10 drops.

   Instruct the patient to take 5 mL of this formula every 2–4 hours,
4. Instruct the patient to eat at least 5–10 fresh cloves of garlic per day.
5. Tell the patient to follow all other directions under mild cutaneous infections above.

For internal MRSA infections

1. Tell the patient to follow the directions for serious cutaneous infections but leave out any topical applications. If the patient is also on antibiotics, in addition to the recommendations above, tell him or her to drink 5–10 cups of green tea per day and/or eat 2–4 oz of dark chocolate per day but not to consume these within 1 hour of intake of oral antibiotics. Explain that this precaution is to avoid a small risk of decreased absorption of the drug that results from the tannins in these medicinal plants. Advise the patient also to take at least 50 billion organisms of probiotics per day and eat fermented foods.

*Blaser G, Santos K, Bode U, et al. Effect of medical honey on wounds colonised or infected with MRSA. J Wound Care 2007;16:325–328.

†Cooper RA, Molan PC, Harding KG. The sensitivity to honey of gram-positive cocci of clinical significance isolated from wounds. J Appl Microbiol 2002;93:857–863.

‡Nostro A, Blanco AR, Cannatelli MA, et al. Susceptibility of methicillin-resistant staphylococci to oregano essential oil, carvacrol and thymol. FEMS Microbiol Lett 2004;230:191–195.

¶Luo MF, Shen Q, Zhang T, Xu YH. Effect of atractylodes rhizome oil and other volatile oils on percutaneous absorption of baicalin [in Chinese]. Zhong Yao Cai 2008;31:1721–1724.

#Davis SC, Mertz PM. Determining the effect of an oak bark formulation on methicillin-resistant *Staphylococcus aureus* and wound healing in porcine wound models. Ostomy Wound Manage 2008;54:16–8,20,22–25.

‖Chusri S, Voravuthikunchai SP. *Quercus infectoria*: A candidate for the control of methicillin-resistant *Staphylococcus aureus* infections. Phytother Res 2008;22:560–562.

**Lee JW, Ji YJ, Yu MH, et al. Antimicrobial effect and resistant regulation of *Glycyrrhiza uralensis* on methicillin-resistant *Staphylococcus aureus*. Nat Prod Res 2009;23:101–111.

ity, cost more to treat, and result in longer hospital stays than other *S. aureus* infections.[3] Despite the notoriety of the rise of MRSA and supposed health care responses to the problem, the rate of infection continues to increase.[4]

Unlike penicillin resistance, which is mediated by β-lactamase that degrades the antibiotic, methicillin resistance results from production of penicillin-binding proteins 2' and 2A mediated by the gene *mecA*.[5] These proteins allow the microbe to avoid not just β-lactamase–resistant methicillin but also standard penicillins, cephalosporins, and carbapenems. Different types of *mecA* are associated with community-acquired (types IV–V) versus hospital-acquired infections (types I–III).[6]

There has been little to no real effort to address the underlying causes of MRSA, which, like other forms of antibiotic resistance, are due in part to the result of antibiotic use.[7–9] Another huge, and still largely ignored, problem is the feeding of the same antibiotics used therapeutically in humans to animals in low doses to promote growth. Recently, this has been linked directly to outbreaks of drug-resistant infections in humans.[10] So, ultimately, MRSA will only be solved by vastly reducing use of antibiotics, particularly removing them from animal feed and decreasing ongoing routine use of antibiotics for patients with viral upper–respiratory tract infections (URIs) that do not respond to these drugs.[11]

Each new antibiotic that has been put forward to treat MRSA infections has resulted in rapid development of resistance to that antibiotic. Linezolid came out in 2000, and within a year, MRSA resistance to this drug was reported.[12] Daptomycin came out in 2003, and by 2005, resistance to this was reported.[13] Vancomycin resistance has already been increasing in MRSA.[14,15] All of these reports suggest that the approach of simply using new antibiotics will not address MRSA, but only ultimately breed an even more powerful and dangerous problem. Herbs offer an alternative.

Ultimately, MRSA will only be solved by vastly reducing use of antibiotics.

Clinical Aspects of MRSA

MRSA can infect tissues all over the body, including skin, muscle, joints, and various organs. Most community-acquired cases are in skin or soft tissue, although there is a growing number of invasive infections.[16] MRSA should be suspected with new-onset inflammatory skin lesions, including impetigo, folliculitis, and furunculosis, that are very severe or therapy resistant. Patients with rapidly spreading infections, or those associated with systemic symptoms such as weakness, fever, myalgia, and/or anorexia, should be referred to an emergency (ER) room to avoid the risk of sepsis or invasive infection.

There is some indication that patients who have taken antibiotics, who have recent trauma, who have recently been hospitalized, who work in health care, or who are in other institutional settings in which infections readily spread (e.g., daycare centers, nursing homes, or locker rooms) are at higher risk of MRSA infections.

Green Tea

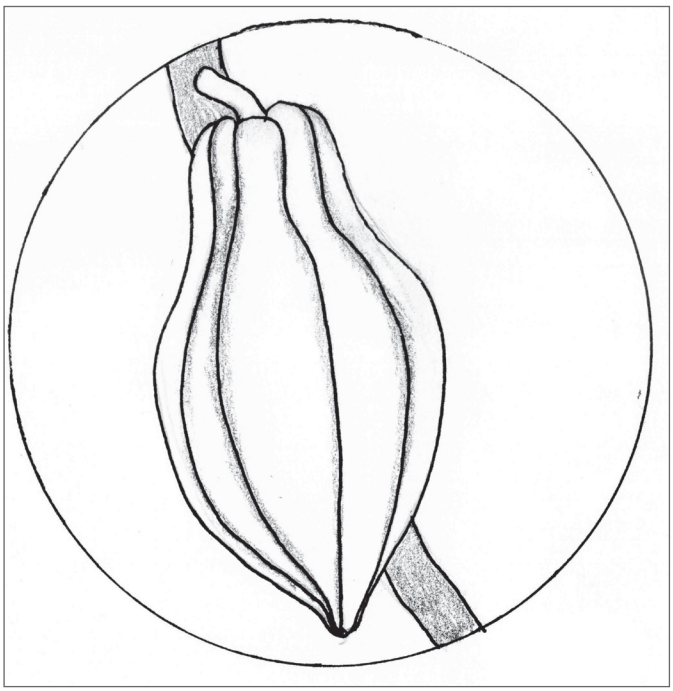
Camellia sinensis (green tea) leaf and extracts thereof act in multifaceted ways against MRSA. Green tea is also one of the few herbs that has been subjected to an actual clinical trial suggesting synergy with antibiotics in humans infected with MRSA. A case study originally suggested that aerosolized green tea could help resolve severe MRSA infections, in this situation, one involving the trachea.[17]

In a randomized preliminary trial, 24 elderly Japanese patients with MRSA in their sputum were given either 2 mL of a solution of green-tea catechins (with a concentration of 3.7 g/L) three times daily by nebulizer for 4 weeks, or mixed into saline and bromhexine on a similar dose schedule.[18] It was unclear whether these patients were all being simultaneously treated with antibiotics. MRSA clearance was significantly greater in the green-tea group, and the subjects in this group were also able to leave the hospital significantly sooner than those in the control group. No adverse effects occurred.

This study was followed by a larger randomized trial of similar design involving 72 disabled, elderly Japanese patients with MRSA in their sputum.[19] After 1 week of treatment, significantly more patients in the green-tea group had reduced or cleared MRSA from their sputum than the patients in the control group (17/36 versus 5/33). Again, it was unclear whether these patients were simultaneously taking antibiotics. No adverse effects occurred in this trial. While clearly these trials are not completely definitive, they do suggest that nebulized green tea is a potentially safe way to help people with respiratory MRSA infections.

Green tea acts in many different ways against MRSA. Several green tea compounds show a range of resistance-modulating effects. Epigallocatechin gallate (EGCG) has inhibited β-lactamase in vitro and was synergistic with various β-lactam antibiotics.[20] Methicillin would not necessarily be needed if the underlying resistance of MRSA to older penicillin-type drugs was addressed.

Combined with oxacillin in vitro, epicatechin gallate (ECG) from green tea markedly lowered the minimum inhibitory concentration (MIC) of the antibiotic against MRSA.[21,22] The gallate moiety of various polyphenols in green tea was determined to be essential for inhibiting β-lactamase and reversing antibiotic resistance in MRSA in vitro.[23] EGCG also lowered the MIC of MRSA to ampicillin and sulbactam to the point that resistance to these drugs was abrogated.[24] EGCG has also been shown to lower the MIC of imipenem, panipenem, and meropenem against MRSA to the point that it became sensitive to these drugs.[25]



Theobroma cacao (chocolate) fruit. Drawing © 2009 by Kathy Abascal, J.D., R.H.(AHG).

Green tea blocks efflux pumps that normally remove various antibiotics from MRSA. For example, EGCG inhibited tetracycline efflux from staphylococci by way of the Tet(K) and Tet(B) pumps.[26] EGCG was active at concentrations more than half its own MIC of 100 mcg/mL. Caution is warranted if green tea is combined with glycopeptide antibiotics such as vancomycin, as one in vitro trial suggested purified EGCG could directly interfere with the action of these drugs.[27]

Green tea, EGCG, and theaflavin also produce inherent, direct, antimicrobial activity against MRSA.[28] EGCG has been reported to disrupt cell-wall components and inhibit DNA gyrase in *S. aureus* in vitro.[29,30] EGCG inhibits staphylococcal gelatinase, an enzyme it uses to spread through tissues, and thus green tea may also limit microbial invasiveness.[31] EGCG is removed from many bacterial cells by the multidrug resistance (MDR) pump, however, which limits EGCG's antimicrobial activity.[32] (Note: The exact same pump is present in other bacteria and cancer cells.) Some researchers might argue that this would make EGCG as an isolated constituent that is useless or doomed to the same fate as single molecular entity antibiotic drugs. However, catechin gallate in whole green tea inhibits MDR and could be expected to preserve at least some of EGCG's activity.[33] This inhibition could also reduce multidrug resistance in bacteria in general, thus enhancing the efficacy of antibiotics.

It has been observed that, when EGCG oxidizes—which it does rapidly in most solutions regardless of pH—it loses activity. The combination of vitamin C with EGCG in vitro enhanced the antibacterial and resistance-modulating activities of EGCG against MRSA.[34] It should be noted that intact green tea is naturally fairly rich in vitamin C, arguing for the synergy of using the whole plant. However, other research has shown that EGCG oxidation products, particularly the major one known as theasinensin A, do still have resistance-modulating effects against MRSA.[35]

Green tea, given all these advantages, should be strongly considered in the protocol for any patient with a MRSA infection. The herb can be delivered as an infusion (1–5 g/cup of water, several cups/day), powder in capsules (10–15 g/day), topically in cream or ointment, or by nebulization of infusion or extracts dissolved in water.

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Dark Chocolate

One alternative to green tea is *Theobroma cacao* (chocolate), as it contains significant levels of EGCG and other important molecules found in tea. Some research suggests that chocolate is even richer in these molecules than green tea.[36] Therefore, it is reasonable to consider 2–4 oz of dark chocolate (at least 60% cocoa solids, but probably greater than 75% would be ideal) per day as a way to reduce antibiotic resistance in MRSA at the very least. This chocolate should not be taken at the exact same time as the antibiotics, as chocolate's tannins might interfere with absorption of the antibiotics. We have seen this approach to be effective in at least one case of a patient with recurrent cellulitis of the legs, at least some instances of which were strongly suspected of being a result of MRSA (the patient did not have sufficient resources to afford cultures to verify this). Previously, dicloxacillin had not worked on some occasions when this patient took it alone, but it worked when the patient took it with dark chocolate.

Tea Tree and Other Volatile Oils

A more directly antimicrobial approach to MRSA, using natural products, emphasizes volatile oils. These highly concentrated (more than 1000 times more concentrated than in the crude herb) extracts were historically made by steam distillation and so contain compounds altered by heat. Newer supercritical carbon-dioxide extracts are not altered by heat and cannot be said to be equivalent to steam-distilled oils, although these extracts may still be very appropriate for use.

Melaleuca alternifolia (tea tree) leaf from Australia provides a powerful volatile oil that has the most clinical and preclinical research in this category. A major issue with MRSA is that some people act as asymptomatic carriers of the organism,

spreading it to other susceptible people or setting themselves up for recurrent infections.

In a randomized trial, 114 hospital patients who were MRSA carriers were treated with standard antimicrobials (mupirocin 2% intranasal ointment, chlorhexidine soap, and silver sulfadiazine ointment) and compared with 110 patients treated with 10% tea tree cream intranasally and a 5% tea tree oil body wash.[37] Both groups were treated for 5 days. Both treatment regimens were equally effective for reducing MRSA carriage. Mupirocin was significantly more effective than tea tree oil for clearing nasal carriage.

Tea tree oil at a 5% concentration is bactericidal against biofilms of MRSA in vitro.[38] Topical tea tree combined with *Pelargonium sidoides* (African geranium) volatile oil infused into a multilayered wound dressing produced strong anti-MRSA activity in vitro.[39] However, when MRSA in culture is habitually exposed to sublethal concentrations of tea tree oil, it becomes increasingly resistant to it.[40] Unfortunately, this also appears to raise the resistance of the organism to other antibiotics, including mupirocin, which is frequently used to treat MRSA infections or to eliminate carriage of the organism.[41]

The current trend toward putting antimicrobial volatile oils in soap, hand lotion, and other products is, therefore, not a particularly good idea, as it is very likely that these oils will simply lead to development of resistance in bacteria just as has been seen with isolated chemicals. These data also strongly suggest that only medicinal doses of tea tree oil should be delivered, and only for as long as necessary, to avoid the development of resistance.

Full-strength, or as minimally diluted as possible (to tolerance), tea tree oil applied topically several times a day to MRSA skin infections is recommended. On sensitive tissues, tea tree oil should be diluted with jojoba or some other hypoallergenic carrier by at least 50%. Internally 2–5 drops of tea tree oil can be taken 4–5 times per day by people with normal liver and kidney function as part of an anti-MRSA protocol.

Some other volatile oils that have shown anti-MRSA activity in vitro and that might be appropriate to combine with tea tree oil include African geranium mentioned above, *Cymbopogon flexuosus* (lemongrass), *Thymus capitatus* (thyme)—especially from flowering tops—and *Lavandula* spp. (lavender).[42–44] All of these can be used topically and internally in similar doses to tea tree. All volatile oils are very concentrated and potentially dangerous and should be used with caution and only by practitioners trained in their use.

Resistance Modulators

In some cases, antibiotics are required because of the severity of the MRSA infection. In these situations, certain herbs are used in combination with antibiotics to enhance their efficacy and directly reduce antibiotic resistance. Green tea and chocolate have already been mentioned as excellent choices for this kind of treatment. A few recently researched herbs are specific to MRSA, although we have more-extensively reviewed the data on antimicrobial resistance modulators elsewhere.[45]

Ginsenosides from *Panax ginseng* (Asian ginseng) root have been mildly antistaphylococcal in vitro (MIC 100 mcg/mL) and significantly synergistic with cefotaxime and kanamycin against MRSA strains (reducing their MICs 2–20-fold).[46] Given Asian ginseng's positive effects on the immune system, this herb might offer additional benefits. This effect has been demonstrated with a close cousin, *Panax quinquefolius*

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(American ginseng), an extract of the root that helps prevent colds and flus.[47] Each of these herbs has a long history of use and is reasonable to consider for treating patients who have MRSA infections. A typical dose is 1–3 g of powdered root three times per day or 3–5 mL of tincture three times per day. Trials should be done to determine the immune and resistance modulating-effects of Asian and American ginseng in patients with MRSA.

Geranium caespitosum (pineywoods geranium) contains compounds that appear to inhibit NorA efflux pumps in MRSA.[48] These compounds (at concentrations under 6.25 mcg/mL) potentiate the activity of quinolone antibiotics such as ciprofloxacin as well as the natural antimicrobial compounds berberine and rhein against *S. aureus* in vitro. Many other species of geranium with similar chemistry exist and thus might also be useful.

Rosmarinus officinalis (rosemary) leaf, in particular its diterpenoids, has inhibited multiple antibiotic efflux pumps in MRSA strains in vitro including erythromycin and NorA multidrug pumps.[49] In another study, researchers were not able to demonstrate antibiotic–rosemary synergy in vitro, and in fact, showed that rosemary lowered the efficacy of ciprofloxacin.[50] The MICs noted by these researchers were also radically different from those mentioned in other literature (60 versus < 5 mg/mL).[51]

Reconciling this wildly different study with others is difficult at best. Most other studies show that rosemary produces significant inherent antimicrobial activity of its own, including against staphylococcal species.[52] A nonantimicrobial relative in the same family (Lamiaceae), *Lycopus europaeus* (bugle weed) herb has similar pump-inhibiting diterpenoids as rosemary. Extracts of this herb effectively lower the MIC of various antibiotics against MRSA in vitro.[53,54]

Garlic

Another antimicrobial food/herb recommended by many practitioners for patients with MRSA infections is *Allium sativum* (garlic) bulb. There is substantial evidence in the literature that garlic bulb can directly kill MRSA, at least this effect has been seen in vitro and in mice.[55,56] No clinical

trials are yet available. A typical recommendation is for a patient with a MRSA to eat 5–10 fresh cloves of garlic per day. This may be intolerable to some people, but lower doses are not sufficient for such a severe infection. Patients should be cautioned that cooking garlic reduces its antimicrobial properties significantly.

Conclusion

Research on herbs to prevent or treat MRSA infection is a burgeoning field with many promising early results. Besides having their own intrinsic activity, herbs also offer interesting possibilities when combined with antibiotics to restore activity.[54] While much more research is needed, clinicians do now clearly have some natural options to add to their approach to infections with this dangerous organism. ■

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