REVIEW ARTICLE

A Comprehensive Review of Herbal Supplements Used for Persistent Symptoms Attributed to Lyme Disease

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Abstract

Context: Lyme disease is the most common, tick-borne disease in the USA. While most patients successfully recover with antibiotics, some patients experience persistent symptoms for months to years. Patients who attribute chronic symptoms to Lyme disease commonly use herbal supplements. The complexity, variability in dose and formulation, and lack of data for these herbal compounds make it difficult to assess their efficacy and safety.

Objective: This review examines the evidence for the antimicrobial activity, safety, and drug-drug interactions of 18 herbal supplements that patients commonly use for treatment of persistent symptoms attributed to Lyme disease.

Design: The research team performed a narrative review by searching the PubMed, Embase, Scopus, Natural Medicines databases, and NCCIH website. The search used the keywords for 18 herbal compounds: (1) andrographis (Andrographis paniculate), (2) astragalus (Astragalus propinquus), (3) berberine, (4) cat's claw bark (Uncaria tomentosa), (5) cordyceps (Cordyceps sinensis), (6) cryptolepis (Cryptolepis sanguinolenta), (7) Chinese skullcap (Scutellaria baicalensis), (8) garlic (Allium sativum), (9) Japanese knotwood (Polygonum cuspidatum), (10) reishi mushrooms (Ganoderma lucidum), (11) sarsaparilla (Smilax medica), (12) Siberian ginseng (Eleutherococcus senticosus), (13) sweet wormwood (Artemisia annua), (14) teasle root (Dipsacus fullonum), (15) lemon balm (Melissa officinalis), (16) oil of oregano (Origanum vulgare), (17) peppermint (Mentha x piperita), and (18) thyme (Thymus vulgaris). The team also searched for terms related to protocols, including Dr. Rawls' protocol and the Buhner protocol.

Setting: University of Maryland Medical Center, Baltimore MD.

Results: Seven of the 18 herbs reviewed had evidence for in-vitro activity against *B. burgdorferi*. These compounds included: (1) cat's claw (2) cryptolepis, (3) Chinese skullcap, (4) Japanese knotweed, (5) sweet wormwood, (6) thyme, and (7) oil of oregano. With the exception of oil of oregano these compounds also have anti-inflammatory activity. In vivo data and clinical trials are lacking. Clinicians should be cautious as many of the identified compounds have drug interactions and additive effects that could lead to increased risks for bleeding, hypotension, and hypoglycemia.

Conclusions: Many of the herbs that alternative and integrative practitioners use to treat Lyme disease have anti-inflammatory effects that may contribute to patients' perceptions of symptomatic improvement. Some herbs have limited demonstrated anti-borrelial activity in vitro, but in-vivo data and clinical trial data is lacking. Further research is required to determine the efficacy, safety and appropriate use of these herbs for this patient population.

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Lyme disease is the most common, tick-borne disease in the USA. The deer tick Ixodes scapularis transmits the causative agents: *Borrelia burgdorferi* (*B. burgdorferi*) and *Borrelia mayonii* (*B. mayonii*). It's estimated that up to 476 000 people contract Lyme disease each year.[1] Medical practitioners successfully treat the majority of patients with Lyme disease with antibiotic therapy. However, some patients develop posttreatment Lyme disease syndrome (PTLDS), and they can experience persistent symptoms for months to years.

The *2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease* from the Infectious Diseases

Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR) provide the proposed criteria for PTLDS, including a history of appropriately treated Lyme disease and the subjective symptoms, such as fatigue, musculoskeletal pain, and cognitive difficulties, that can appear within six months of a patient's diagnosis with Lyme disease and for at least six months after antimicrobial therapy.[2]

Some use the term chronic Lyme disease (CLD), including Lyme-literate medical doctors (LLMDs), patient advocacy groups, and the public. While the term includes patients with PTLDS, it also includes many misdiagnosed patients with similar, nonspecific, symptom complexes for which no convincing evidence exists for infection with *B. burgdorferi*.

Regardless of the differences in PTLDS, CLD, and misdiagnosed Lyme groups, patients in these groups attribute their symptoms to Lyme disease, but they differ in the presence or absence of a documented Borrelia infection.

Effective treatment for these symptoms is unknown. The guidelines mentioned above discuss several randomized clinical trials that have shown that prolonged antibiotic therapy is not useful for patients with PTLDS.[2] In his review, Cameron examined clinical studies that have shown that PTLDS patients have reported higher rates of depression and arthralgia and lower health-related quality of life as compared to the general US population.[3] Ali et al found that these patients also demonstrate a lack of satisfaction with conventional healthcare and use of alternative therapies and practitioners, such as integrative-medicine physicians, LLMDs, naturopaths, and acupuncturists.[4]

PTLDS, CLD, and misdiagnosed Lyme patients commonly use herbal supplements for Lyme disease as well as alternative and integrative healthcare providers for the following purposes: (1) to eradicate bacteria, (2) to boost the immune system, (3) to decrease inflammation, and (4) to decrease symptoms and improve quality of life.

These patients use the herbs as single agents and in combination as part of treatment protocols. The herbs are readily available and are well known in the CLD community. The complexity, variability in dose and formulation, and lack of data for these herbal compounds make it difficult to assess their efficacy and safety.

Although researchers have not studied in depth the mechanism responsible for the perceived improved outcomes in humans, they have studied many of the compounds for their effectiveness against bacterial and viral infections as well as their anti-inflammatory and other properties in vitro.

This review intended to examine the available evidence for the efficacy, safety, and drug-drug interactions for 18 herbal supplements that patients commonly use for treatment of persistent symptoms attributed to Lyme disease.

Methods

The study took place at the University of Maryland Medical Center, Baltimore MD. The research team performed a narrative review by searching the PubMed, Embase, Scopus, Natural Medicines databases, and NCCIH website. The research team also reviewed bibliographies from selected articles.

The team based the choice of therapies on their experience with patients at an academic Lyme center, an internet search of patient's testimonials, and a literature search using the following terms for 18 herbal compounds: (1) andrographis (Andrographis paniculate), (2) astragalus (*Astragalus propinquus*), (3) berberine, (4) cat's claw bark (*Uncaria tomentosa*), (5) cordyceps (*Cordyceps sinensis*), (6) cryptolepis (Cryptolepis sanguinolenta), (7) Chinese skullcap (*Scutellaria baicalensis*), (8) garlic (*Allium sativum*), (9) Japanese knotwood (*Polygonum cuspidatum*), (10) reishi mushrooms (*Ganoderma lucidum*), (11) sarsaparilla (*Smilax medica*), (12) Siberian ginseng (*Eleutherococcus senticosus*), (13) sweet wormwood (*Artemisia annua*), (14) teasel root (*Dipsacus fullonum*), (15) lemon balm (*Melissa officinalis*), (16) oil of oregano (*Origanum vulgare*), (17) peppermint (*Mentha x piperita*), and (18) thyme (Thymus vulgaris). The team also searched for terms related to protocols, including Dr. Rawls' protocol and the Buhner protocol.

The review includes articles published in the English language. A total of 514 references were identified from the database searches. Duplicate publications were removed, which left the team with 437 publications. Publications were reviewed for information about safety, efficacy, and drug-drug interactions for the 18 identified compounds. Publications which did not contain relevant information were not included in the review.

The evaluation consisted of a review: (1) of the herbs' antimicrobial activity, antiborrelia activity, anti-inflammatory, and other relevant symptomatic activity as well as supportive care, and (2) safety data, status as generally recognized as safe (GRAS), and clinically relevant drug-drug interactions.

Results

Table 1 outlines the categories for each compound's evidence include: (1) activity = +, (2) no activity = -, and (3) mixed activity = +/-.

Antimicrobial Activity

Thirteen of the eighteen herbs had evidence of antimicrobial activity in vitro; three had mixed or weak data, and two had no data.[5-27] The thirteen with antimicrobial activity in vitro were: (1) astragalus, (2) berberine, (3) cat's claw, (4) cordyceps, (5) cryptolepis, (6) Chinese skullcap, (7) garlic, (8) Japanese knotweed, (9) sweet wormwood, (10) reishi mushrooms, (11) lemon balm, (12) peppermint, (13) oil of oregano. The research team found inconclusive data regarding the antimicrobial

Table 1. Activity of Herbal Compounds Commonly That Patients Use for Lyme Symptoms. the categories for each compound's evidence include: (1) activity = +, (2) no activity = -, and (3) mixed activity = +/-[4-40]

Common Name	Antibacterial	Anti-borrelia	Anti-inflammatory	Symptomatic (Other)
Andrographis[5,6,14]	+/-	-	+	+
Astragalus[15,30]	+	-	+	+
Berberine[16,41]	+	-	+	+
Cat's claw[5,17]	+	+	+	+
Cordyceps[18,31]	+	-	+	+
Cryptolepis[5,19]	+	+	+	+
Chinese skullcap[5,20,28]	+	+	+	+
Garlic[21,22]	+	-	+	+
Japanese knotweed[5,7,8]	+	+	+	+
Sweet wormwood[5,9,10,29,32,54]	+	+	+	+
Reishi mushrooms[23]	+	-	-	+
Sarsaparilla[11,24]	+/-	-	+	+
Siberian ginseng[25]	-	-	+	+
Teasel root[13]	-	-	-	-
Lemon balm[5,33,34]	+	-	+	+
Peppermint[5,26,35-37]	+	-	+	+
Thyme[13,27,38,39]	+/-	+	+/-	+
Oil of oregano[12,40]	+	+	-	-

activity of Andrographis, sarsaparilla, and thyme. No supporting evidence existed for antimicrobial activity in Siberian ginseng and teasel root.

Anti-borrelia Activity

Seven of the 18 herbs reviewed had evidence for in-vitro activity against *B. burgdorferi*. These compounds included: (1) cat's claw,[5] (2) cryptolepis,[5] (3) Chinese skullcap,[5] (4) Japanese knotweed,[5] (5) sweet wormwood,[5] (6) thyme,[5,13] and (7) oil of oregano.[12]

Recently, Feng et al investigated the anti-borrelia activity of 15 commonly used botanical medicines and three other natural antimicrobial agents, five of which were of interest for this review.[5] Those researchers evaluated the compounds' activity against growing and stationary cultures of *B. burgdorferi*, and they used antibiotic controls, cefuroxime and doxycycline. The researchers' analysis included: (1) calculating the minimal inhibitory concentration (MIC); (2) determining the residual viability of the stationary phase at different herbal concentrations—1%, 0.5%, 0.25%; and (3) subculturing at 1% and 0.5%. Seven of the compounds studied demonstrated more activity against the stationary phase of *B. burgdorferi* compared to controls. Those compounds included cryptolepis, black walnut (*Juglans nigra*), Japanese knotweed, sweet wormwood, cat's claw, Cistus incanus, and Chinese skullcap.

Those researchers also determined that Japanese knotweed and cryptolepis were the most potent against the replicating organism, with the lowest MICs, at MIC = 0.03-0.06% and MIC = 0.25-0.5%, respectively. Sweet wormwood, black walnut, and cat's claw resulted in higher MICs, despite their antimicrobial activity against the non-growing forms. While compounds such as black walnut demonstrated activity, the researchers noted the clinically relevant side effect of skin pigmentation. The study also noted, in contrast to previous studies or to assumed anti-borrelia activity, that some of the commonly used products had little or no activity against *B. burgdorferi*: andrographis, stevia, grapefruit seed extract, Dipsacus spp, colloidal silver, monolaurin, and ashwagandha.

The other two compounds with evidence of anti-borrelia activity were oregano and thyme. Previously in 2017, Feng et al demonstrated in-vitro activity for oregano against *B. burgdorferi*.[12] Those researchers identified oregano as one of the most active essential oils in vitro given its complete eradication of the stationary phase of *B. burgdorferi*, even at a 0.05% concentration. Conversely, that study didn't show any significant anti-borrelia activity for peppermint. In 2019, Goc et al demonstrated that thyme at a 0.2% concentration had bactericidal activity against spirochetes.[13]

It's important to note that all studies reviewed for anti-borrelia activity were in vitro. Determination of clinical relevance requires further studies.

Symptomatic Activity

The correlation and underlying mechanism of symptoms that patients with PTLDS and CLD experience are unknown. These symptoms include fatigue or lethargy, musculoskeletal pain, arthritis-like pain, and decreased cognition or clarity. A common property of the herbs that the current review studied was anti-inflammatory activity.

Almost all the compounds, 15 out of 18, had documented anti-inflammatory properties[6,8,9,11,15,16-19,22,28,35,36,38] Of those, five were among the previously described compounds that exhibited good anti-borrelia activity in vitro: Cat's claw, cryptolepis, Japanese knotweed, sweet wormwood, and thyme.

Andrographis, astragalus, berberine, cordyceps, garlic, sarsaparilla, and peppermint lack anti-borrelia activity but possess potent anti-inflammatory properties.[6,11,15,16,18,41] Oil of oregano was the only herb found to have a significant anti-borrelia activity that lacked any evidence of anti-inflammatory properties.

In addition to anti-inflammatory effects, some of the herbal compounds had potential benefits for other common symptoms of PTLDS and CLD. In a human clinical trial, Piscoya et al found that cat's claw and Chinese skullcap had benefits for the treatment of pain and joint swelling in patients with osteoarthritis.[42] Cat's claw may also improve fatigue.[43] In a human clinical trial, Krebs et al studied sweet wormwood and found that it demonstrated a steroid-sparing effect in Crohn's disease.[29] Puri et al studied its synthetic analog, artesunate, for patients with Lyme disease and found improvement with short-term memory.[44]

Specific Compounds

As mentioned above, five herbal supplements and two essential oils demonstrated evidence for anti-borrelia activity in vitro. The compounds identified were Cat's claw, cryptolepis, Chinese skullcap, Japanese knotweed, sweet wormwood, thyme, and oregano.

Cat's Claw

Medical practitioners have used cat's claw for inflammatory conditions for more than 2000 years.[30] Cat's claw has demonstrated antimicrobial and anti-borrelia activity in vitro.[5] It's also an effective antioxidant and exerts potent anti-inflammatory effects as an immunomodulator via suppression of tumor necrosis factor alpha (TNF-α).[45]

Preliminary clinical studies in humans have shown decreased pain for patients with osteoarthritis and a reduced number of painful and swollen joints in patients with rheumatoid arthritis in combination with standard treatment.[42] In a prospective trial, cat's claw found an increase in quality of life, social functioning, and fatigue for patients with advanced solid tumors.[43]

Those three studies point to a modest benefit but are limited by small sample sizes (n = 40-51) and specific disease states. In terms of safety, Cat's claw may be safe when used orally for a short period of time and may be associated with gastrointestinal adverse effects.[30,43]

Cryptolepis

Medical practitioners have used Cryptolepis sanguinolenta to treat malaria, diarrhea, and various respiratory conditions.[19] Feng et al found that Cryptolepis can have antibacterial and anti-borrelia activity in vitro.[7]In a single animal study, Cryptolepis demonstrated analgesic and anti-inflammatory effects in rat-paw edema.[19] Closely related Cryptolepis buchanani has demonstrated in-vivo analgesic, anti-inflammatory, and chondroprotective effects.[46]

The full toxicity profile of Cryptolepis is unknown, but it has caused significant safety concerns in terms of antifertility effects and reproductive toxicity. Animal studies have shown that Cryptolepis may effect human reproductive systems.[19]

Chinese Skullcap

Traditional Chinese medicine has used Chinese skullcap as immune support and for various conditions, such as psychiatric disorders, anxiety, seizures, osteoarthritis, viral infections.[30] Baicalein and baicalin are two flavonoids commonly isolated from the Scutellaria genus.

Chinese Skullcap has demonstrated antibacterial, anti-borrelia, and anti-inflammatory activity in vitro.[5,20,28] Two studies demonstrated neuroprotective effects for baicalein, a flavonoid commonly isolated from the Scutellaria genus, in vivo and in vitro, and suggested that it may benefit patients with Parkinson's disease.[47,48] While its neuroprotective effects have been demonstrated in vivo and in vitro, those effects have yet to be evaluated in human clinical studies.[49] Dinda et al found anti-inflammatory effects for baicalin in-vitro.[28]

Flavocoxid, a medical food as established by the Food and Drug Administration (FDA), is a compound of two flavonoids, baicalin (*Scutellaria baicalensis*) and catechin (*Acacia catechu*). Levy et al found that flavocoxid, when compared to naproxen, can be effective in treating the symptoms of osteoarthritis.[50] Additionally, Arjmandi et al found that it can decrease perceived pain and stiffness in osteoarthritis of the knee.[51] Flavocoxid has documented clinical safety but may cause sedation and acute liver toxicity.[52]

Japanese Knotweed

Japanese knotweed, also known as hu zhang, originates in Asia. It contains two active constituents, hydroxyanthraquinone and resveratrol. Traditional medicine has used it for various ailments, including wound healing.

Japanese knotweed has demonstrated antibacterial, anti-borrelia, and anti-inflammatory activity in vitro.[5,7,8] A review of several studies found evidence for antitumor, neuroprotective, and cardioprotective effects in animals, but no human clinical studies have occurred to date.[7] Insufficient safety data exists for Japanese knotweed due to the lack of clinical data, but a human study of trans-resveratrol showed minimal toxicity with some gastrointestinal upset.[7]

Sweet Wormwood

Sweet wormwood is native to Europe, and traditional medicine has used it for over 2000 years. The herb has demonstrated antibacterial and anti-borrelia in vitro.[5] In patients with Crohn's disease, it has demonstrated anti-inflammatory activity in a small clinical study and a steroid-sparing effect in a double-blind study.[29]

Tu Youyou for her study of sweet wormwood's active antimalarial constituent, artemisinin, received the 2015 Nobel Prize.[53] In a small pilot study, the synthetic analog of the active constituent, artesunate, provided significant improvement in the short-term memory of patients with Lyme disease when combined with IV ceftriaxone.[44]

Full understanding of the effects of sweet wormwood on persistent symptoms attributed to Lyme disease requires a randomized controlled trial. Limited safety data exists for it. Omer et al demonstrated that it's safe for up to 6 months with some mild gastrointestinal upset at higher doses.[54] Of note, drinking wormwood oil purchased on the internet has been associated with numerous cases of acute renal failure.[55]

Oregano and Thyme

People have cultivated oregano and thyme for culinary purposes. Both compounds have demonstrated antibacterial and anti-borrelia activity.[5,12] Preuss et al studied the active constituent in oregano, carvacrol, in mice and found that it was a useful agent against *Staphylococcus aureus*; however, testing related to human infections has yet to occur.[56]

Oil of oregano lacks evidence of anti-inflammatory or other symptomatic activity. However, thyme may have some anti-inflammatory effects due to its ability to scavenge free radicals.[30] Both compounds have GRAS status when consumed in common amounts used in food, but insufficient evidence exists of their safety in high amounts.

Safety and Drug-Drug Interactions (DDI)

The importance of a thorough and comprehensive medication review for patients with PTLDS, CLD, or misdiagnosed Lyme can not be overstated. Polypharmacy in this population is common due to numerous comorbid conditions. An evaluation of the risk for drug-drug interactions is important when counseling patients.

The current review used the Natural Medicines Comprehensive Database to identify potential drug-drug interactions for the 18 compounds discussed above. The current research team considered the interactions' ratings and severity when deciding what interactions to include. Table 2 summarizes the results.

It's important to note that drug-drug interaction data for these compounds is in its infancy. The majority of the interactions are possible, with minimal data to fully elucidate the extent of the interaction. Clinicians should be particularly cautious in patients requiring medications for anticoagulation, hypertension, and diabetes as many of the identified compounds have additive effects and could lead to increased risks for bleeding, hypotension, and hypoglycemia. Patients for whom medical practitioners deem that the benefits for these compounds outweigh the risks should receive counseling to monitor for potential adverse effects related to DDIs.

Discussion

Many areas of controversy exist with respect to the treatment of Lyme disease. At the crux of the controversy is the issue of whether *B. burgdorferi* can cause a chronic, persistent infection. Researchers have proposed morphologic variants of *B. burgdorferi*, described as L-forms, cyst forms, spheroplasts or round bodies, and biofilm-like colonies, as causative agents of the persistent symptoms in CLD patients.

It should be noted that many other bacteria can assume these L-forms under certain conditions and can produce biofilms. A systematic literature review of morphologic variants did not support the role of *B. burgdorferi* variants in causing chronic persistent infection.[57]

To the current research team's knowledge, no human clinical studies have occurred that show a causative link between variants or between *B. burgdorferi* biofilms and persistent clinical disease. However, that link has been the basis for prolonged use of antibiotics and herbal supplements for anti-borrelia eradication by alternative practitioners who provide care to patients experiencing persistent symptoms attributed to Lyme disease.

Patients use many of the herbs reviewed in this article alone or in combination for an antimicrobial effects as well as for other reasons. The current review has demonstrated that some of the herbs that PTLDS, CLD, and misdiagnosed Lyme patients use for relief of persistent symptoms do have in-vitro activity against *B. burgdorferi*, but many do not.

The current review found that Cat's claw, Cryptolepis, Chinese skullcap, Japanese knotweed, sweet wormwood, thyme, and oil of oregano can have anti-borrelial activity in vitro; however, their clinical efficacy against *B. burgdorferi* hasn't been assessed, and therefore, their role in therapy is unclear.

It's worth noting that many herbal medicines for HIV have been shown to have in vitro activity, but none of them have translated into effective antiviral therapy comparable to conventional antiretroviral therapy. Some herbs have shown antimicrobial activity but no anti-borrelial activity, such as peppermint, highlighting the fact that the extrapolation of antimicrobial activity in general may not translate into antimicrobial activity against Borrelia.

In addition, bacteria may develop resistance to essential oils after exposure. However, researchers have not studied the antimicrobial resistance of *B. burgdorferi* to these herbs, so it is unclear for what period they would have in-vitro efficacy after exposure. The effects of these herbs on the gastrointestinal (GI) microbiome is also unclear.

The symptoms that PTLDS, CLD, and misdiagnosed Lyme patients with chronic symptoms have attributed to Lyme disease include fatigue, musculoskeletal pain, cognitive issues, poor sleep, and mood issues. Almost all of the herbs reviewed have anti-inflammatory effects with the exception of oil of oregano and reishi mushrooms.

Table 2. Common Drug-drug Interactions of Herbal Compounds Commonly That Patients Use for Lyme Symptoms

Common Name	Drug Class Interactions	Mechanism for Drug Interaction	Medications to Avoid
Andrographis[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Antihypertensive	Additive hypotension effects	ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics
Astragalus[30]	Lithium	Decreased excretion resulting in increased lithium concentrations	
Berberine[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Antidiabetes medications	Additive blood glucose lowering effects	Sulfonylureas, thiazolidinediones, meglitinides, insulin
	Antihypertensive	Additive hypotension effects	ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics
	CNS depressants	Additive sedative effects	Benzodiazepines, opioid analgesics
	CYP2C9 Substrates	Inhibition of CYP2C9, increased substrate concentrations	Fluoxetine, glimepiride, glipizide, irbesartan, losartan, warfarin
	CYP2D6 Substrates	Inhibition of CYP2D6, increased substrate concentrations	Duloxetine, fluoxetine, metoprolol, ondansetron, oxycodone, paroxetine, tramadol, venlafaxine
	CYP3A4 Substrates	Inhibition of CYP3A4, increased substrate concentrations	Amiodarone, atorvastatin, diazepam, methadone, simvastatin, tacrolimus, warfarin
Cat's Claw Bark[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Antihypertensive	Additive hypotension effects	ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics
	CYP3A4 Substrates	Inhibition of CYP3A4, increased substrate concentrations	
Cordyceps[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
Cryptolepis[30]			
Chinese Skullcap[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Antidiabetes medications	Additive blood glucose lowering effects	Sulfonylureas, thiazolidinediones, meglitinides, insulin
	Antihypertensive	Additive hypotension effects	ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics
	CNS Depressants	Additive sedative effects	Benzodiazepines, opioid analgesics
	CYP2C19 Substrates	Inhibition of CYP2C19, increased substrate concentrations	Citalopram, diazepam, phenytoin, warfarin
	Lithium	Decreased excretion resulting in increased lithium concentrations	
Garlic[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Antidiabetes medications	Additive blood glucose lowering effects	Sulfonylureas, thiazolidinediones, meglitinides, insulin
	Antihypertensive	Additive hypotension effects	ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics
	CNS depressants	Additive sedative effects	Benzodiazepines, opioid analgesics
	CYP3A4 Substrates		
Japanese Knotwood[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	CYP2C19 Substrates	Inhibition of CYP2C19, increased substrate concentrations	Citalopram, diazepam, phenytoin, warfarin
	CYP3A4 Substrates	Inhibition of CYP3A4, increased substrate concentrations	
Sweet wormwood[30]	None/ unknown		

Table 2. (continued)

Common Name	Drug Class Interactions	Mechanism for Drug Interaction	Medications to Avoid
Reishi mushrooms[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Antidiabetes medications	Additive blood glucose lowering effects	Sulfonylureas, thiazolidinediones, meglitinides, insulin
	Antihypertensive	Additive hypotension effects	ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide diuretics
Sarsaparilla[30]	Digoxin	Increased absorption, increased concentrations	
	Lithium	Decreased excretion, increased concentrations	
Siberian Ginseng[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Antidiabetes medications	Additive blood glucose lowering effects	Sulfonylureas, thiazolidinediones, meglitinides, insulin
	CYP2D6 Substrates		
	CYP3A4 Substrates	Inhibition of CYP3A4, increased substrate concentrations	
	QTC prolonging medications	Possible increase of the QT interval and increasing the risk of ventricular arrhythmias	Fluoroquinolones, methadone
Teasel Root, teazle[30]	Limited information available		
Lemon balm[30]	Antidiabetes medications	Additive blood-glucose lowering effects	Sulfonylureas, thiazolidinediones, meglitinides, insulin
	CNS Depressants	Additive sedative effects	Benzodiazepines and opioid analgesics
Peppermint[30]	CYP2C19 substrates	Inhibition of CYP2C19, increased substrate concentrations	Fluoxetine, glimepiride, glipizide, irbesartan, losartan, warfarin
	CYP2C9 substrates	Inhibition of CYP2C9, increased substrate concentrations	
	CYP3A4 substrates	Inhibition of CYP3A4, increased substrate concentrations	
Thyme[30]	Anticholinergic	Inhibition of acetylcholinesterase, decreased efficacy of anticholinergic agents	
	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Cholinergic	Increased effects	
	Estrogens	Estrogen-receptor binding activity competitively inhibits the effects of estrogen replacement therapy	
Oil of oregano[30]	Anticoagulant/ Antiplatelet	Additive antiplatelet effects	NSAIDs, warfarin, LMWH, Factor Xa inhibitors, direct thrombin inhibitors
	Antidiabetes medications	Additive blood-glucose lowering effects	Sulfonylureas, thiazolidinediones, meglitinides, insulin

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CYP2C19, cytochrome P450 family 2 subfamily C member 19; CYP2C9, cytochrome p450 family 2 subfamily c member 9 CYP3A4, cytochrome P450 family 3 subfamily A member 4 member; LMWH, low-molecular-weight heparins; NSAIDs, non-steroidal anti-inflammatory drugs.

Notably, researchers have studied cat's claw and Chinese Skullcap in human clinical trials, and they have shown benefits for pain and joint swelling in patients with osteoarthritis.[42,50] Similarly, almost all of the herbs have various symptomatic effects with the exception of teasel root and oil of oregano.

The 2020 guidelines for Lyme disease recommend that early infections be treated with 10-14 days of oral antibiotics; disseminated disease, with cardiac and neurologic involvement, with 14-21 days of intravenous (IV) or oral antimicrobial therapy; and arthritis or severe neurologic disease with 28 days of IV or oral antibiotics.[2] These are the recommended current therapies for Lyme disease, which can decrease risk of permanent infection-related damage.

While some of the herbs show in-vitro anti-borrelial activity, no clinical data exists for humans currently. More important, research has not shown that herbal therapy can prevent the development of the disseminated manifestations of Lyme disease. The authors do not

recommend herbal treatment of Lyme disease attributed to an active infection.

In addition, many of the 18 herbs in the current study, individually and in combination, lack safety data. Drug interactions with anticoagulants, antihypertensives, antidiabetic, antiseizure, and other medications highlight the need for providers to be familiar with these supplements. Physicians and other care providers should ask all patients presenting for a Lyme evaluation about their use of herbal supplements and educate them regarding the lack of in-vivo efficacy, symptomatic effects, and drug interactions.

Conclusions

Many of the herbs that alternative and integrative practitioners use to treat Lyme disease have anti-inflammatory effects that may contribute to patients' perceptions of symptomatic improvement. Some herbs demonstrated limited anti-borrelial activity in vitro, but in-vivo data and clinical trial data is lacking. Further research is required to determine the efficacy, safety and appropriate use of these herbs for the patient population.

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References

1. Kugeler KJ, Schwartz AM, Delorey MJ, Mead PS, Hinckley AF. Estimating the frequency of Lyme disease diagnoses—united States, 2010-2018. *Emerg Infect Dis*. 2021;27(2):616-619. doi:10.3201/eid2702.202731
2. Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis*. 2021;72(1):e1-e48. doi:10.1093/cid/ciaa1215
3. Cameron DJ. Clinical trials validate the severity of persistent Lyme disease symptoms. *Med Hypotheses*. 2009;72(2):153-156. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/19013025 doi:10.1016/j.mehy.2008.09.030
4. Ali A, Vitulano L, Lee R, Weiss TR, Colson ER. Experiences of patients identifying with chronic Lyme disease in the healthcare system: a qualitative study. *BMC Fam Pract*. 2014;15(1):79. Accessed February 25, 2021. http://www.ncbi.nlm.nih.gov/pubmed/24885888 doi:10.1186/1471-2296-15-79
5. Feng J, Leone J, Schweig S, Zhang Y. Evaluation of natural and botanical medicines for activity against growing and non-growing forms of B. burgdorferi. *Front Med (Lausanne)*. 2020;7:6. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631138166 doi:10.3389/fmed.2020.00006
6. Hancke JL, Srivastav S, Cáceres DD, Burgos RA. A double-blind, randomized, placebo-controlled study to assess the efficacy of Andrographis paniculata standardized extract (ParActin®) on pain reduction in subjects with knee osteoarthritis. *Phytother Res*. 2019;33(5):1469-1479. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/30968986 doi:10.1002/ptr.6339
7. Zhang H, Li C, Kwok S-T, Zhang Q-W, Chan S-W. A review of the pharmacological effects of the dried root of Polygonum cuspidatum (Hu Zhang) and its constituents. Evid Based Complement Alternat Med. 2013 [cited 2021 Mar 17]; 2013:208349. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24194779
8. Zahedi HS, Jazayeri S, Ghiasvand R, Djalali M, Eshraghian MR. Effects of polygonum cuspidatum containing resveratrol on inflammation in male professional basketball players. *Int J Prev Med*. 2013;4(suppl 1):S1-S4. Accessed February 25, 2021. http://www.ncbi.nlm.nih.gov/pubmed/23717757
9. Kim KE, Ko K-H, Heo RW, et al. Artemisia annua leaf extract attenuates hepatic steatosis and inflammation in high-fat diet-fed mice. *J Med Food*. 2016;19(3):290-299. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/26741655 doi:10.1089/jmf.2015.3527
10. Kim MH, Seo JY, Liu KH, Kim J-S. Protective effect of Artemisia annua L. extract against galactose-induced oxidative stress in mice. *PLoS One*. 2014;9(7):e101486. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/24988450 doi:10.1371/journal.pone.0101486
11. Lu C-L, Zhu W, Wang M, Xu X-J, Lu C-J. Antioxidant and anti-inflammatory activities of phenolic-enriched extracts of Smilax glabra. Evid Based Complement Alternat Med. 2014 [cited 2020 Nov 5]; 2014:910438. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25477999
12. Feng J, Zhang S, Shi W, Zubcevik N, Miklossy J, Zhang Y. Selective essential oils from spice or culinary herbs have high activity against stationary phase and biofilm Borrelia burgdorferi. *Front Med (Lausanne)*. 2017;4:169. Accessed April 23, 2020. http://www.ncbi.nlm.nih.gov/pubmed/2907562 doi:10.3389/fmed.2017.00169
13. Goc A, Niedzwiecki A, Rath M. Anti-borreliae efficacy of selected organic oils and fatty acids. *BMC Complement Altern Med*. 2019;19(1):40. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/30717726 doi:10.1186/s12906-019-2450-7
14. Burgos RA, Hancke JL, Bertoglio JC, et al. Efficacy of an Andrographis paniculata composition for the relief of rheumatoid arthritis symptoms: a prospective randomized placebo-controlled trial. *Clin Rheumatol*. 2009;28(8):931-946. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/19408036 doi:10.1007/s10067-009-1180-5
15. Zhang W-J, Hufnagl P, Binder BR, Wojta J. Antiinflammatory activity of astragaloside IV is mediated by inhibition of NF-kappaB activation and adhesion molecule expression. *Thromb Haemost*. 2003;90(5):904-914. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/14597987 doi:10.1160/TH03-03-0136
16. Ivanovska N, Philipov S. Study on the anti-inflammatory action of Berberis vulgaris root extract, alkaloid fractions and pure alkaloids. *Int J Immunopharmacol*. 1996;18(10):553-561. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/9080249 doi:10.1016/S0192-0561(96)00047-1
17. Heitzman ME, Neto CC, Winiarz E, Vaisberg AJ, Hammond GB. Ethnobotany, phytochemistry and pharmacology of Uncaria (Rubiaceae). *Phytochemistry*. 2005;66(1):5-29. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/15649507 doi:10.1016/j.phytochem.2004.10.022
18. Shahed AR, Kim SI, Shoskes DA. Down-regulation of apoptotic and inflammatory genes by Cordyceps sinensis extract in rat kidney following ischemia/reperfusion. *Transplant Proc*. 2001;33(6):2986-2987. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/11543822 doi:10.1016/S0041-1345(01)02282-5
19. Osafo N, Mensah KB, Yeboah OK. Phytochemical and pharmacological review of Cryptolepis sanguinolenta (Lindl.) Schlechter. Adv Pharmacol Sci. 2017 [cited 2020 Nov 5]; 2017:3026370. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29750083
20. Ming J, Zhuoneng L, Guangxun Z. Protective role of flavonoid baicalin from Scutellaria baicalensis in periodontal disease pathogenesis: A literature review. *Complement Ther Med*. 2018;38:11-18. Accessed September 11, 2020. http://www.ncbi.nlm.nih.gov/pubmed/29857875 doi:10.1016/j.ctim.2018.03.010
21. Sasaki J, Kita T, Ishita K, Uchisawa H, Matsue H. Antibacterial activity of garlic powder against Escherichia coli O-157. *J Nutr Sci Vitaminol (Tokyo)*. 1999;45(6):785-790. doi:10.3177/jnsv.45.785
22. Ried K. Garlic lowers blood pressure in hypertensive individuals, regulates serum cholesterol and stimulates immunity: an updated meta-analysis and review. *J Nutr*. 2016;146(2)(suppl):389S-396S. doi:10.3945/jn.114.202192
23. Yoon SY, Eo SK, Kim YS, Lee CK, Han SS. Antimicrobial activity of Ganoderma lucidum extract alone and in combination with some antibiotics. *Arch Pharm Res*. 1994;17(6):438-442. doi:10.1007/BF02979122
24. Xu S, Shang MY, Liu GX, et al. Chemical constituents from the rhizomes of Smilax glabra and their antimicrobial activity. *Molecules*. 2013;18(5):5265-5287. doi:10.3390/molecules18055265
25. Vogler BK, Pittler MH, Ernst E. The efficacy of ginseng. A systematic review of randomised clinical trials. *Eur J Clin Pharmacol*. 1999;55(8):567-575. doi:10.1007/s002280050674
26. Işcan G, Kirimer N, Kürkcüoğlu M, Başer KH, Demirci F, Demirci F. Antimicrobial screening of Mentha piperita essential oils. *J Agric Food Chem*. 2002;50(14):3943-3946. doi:10.1021/jf011476k
27. Proestos C, Chorianopoulos N, Nychas GJE, Komaitis M; Investigation of Their Antioxidant Capacity and Antimicrobial Activity. RP-HPLC analysis of the phenolic compounds of plant extracts. investigation of their antioxidant capacity and antimicrobial activity. *J Agric Food Chem*. 2005;53(4):1190-1195. doi:10.1021/jf040083t
28. Dinda B, Dinda S, DasSharma S, Banik R, Chakraborty A, Dinda M. Therapeutic potentials of baicalin and its aglycone, baicalein against inflammatory disorders. *Eur J Med Chem*. 2017;131:68-80. Accessed November 5, 2020. http://www.ncbi.nlm.nih.gov/pubmed/28288320 doi:10.1016/j.ejmech.2017.03.004

29. Krebs S, Omer TN, Omer B. Wormwood (Artemisia absinthium) suppresses tumour necrosis factor alpha and accelerates healing in patients with Crohn's disease - A controlled clinical trial. *Phytomedicine*. 2010;17(5):305-309. Accessed February 25, 2021. http://www.ncbi.nlm.nih.gov/pubmed/19962291 doi:10.1016/j.phymed.2009.10.013
30. Natural Medicines - Professional. [cited 2020 Sep 9]. Available from: https://naturalmedicines.therapeuticresearch.com
31. Li DG, Ren ZX. Cordyceps sinensis promotes immune regulation and enhances bacteriostatic activity of PA-824 via IL-10 in Mycobacterium tuberculosis disease. *Braz J Med Biol Res*. 2017;50(9):e6188. doi:10.1590/1414-431x20176188
32. Yashphe J, Segal R, Breuer A, Erdreich-Naftali G. Antibacterial activity of Artemisia herba-alba. *J Pharm Sci*. 1979;68(7):924-925. doi:10.1002/jps.2600680742
33. Cases J, Ibarra A, Feuillère N, Roller M, Sukkar SG. Pilot trial of Melissa officinalis L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. *Med J Nutrition Metab*. 2011;4(3):211-218. doi:10.1007/s12349-010-0045-4
34. Kennedy DO, Little W, Scholey AB. Attenuation of laboratory-induced stress in humans after acute administration of Melissa officinalis (Lemon Balm). *Psychosom Med*. 2004;66(4):607-613. doi:10.1097/01.psy.0000132877.72833.71
35. Atta AH, Alkofahi A. Anti-nociceptive and anti-inflammatory effects of some Jordanian medicianal plant extracts 1998;60:117-24.
36. Gao M, Singh A, Macri K, et al. Antioxidant components of naturally-occurring oils exhibit marked anti-inflammatory activity in epithelial cells of the human upper respiratory system. *Respir Res*. 2011;12(1):92. doi:10.1186/1465-9921-12-92
37. Ilmberger J, Heuberger E, Mahrhofer C, Dessovic H, Kowarik D, Buchbauer G. The influence of essential oils on human attention. I: alertness. *Chem Senses*. 2001;26(3):239-245. doi:10.1093/chemse/26.3.239
38. Vigo E, Cepeda A, Gualillo O, Perez-Fernandez R. In-vitro anti-inflammatory effect of Eucalyptus globulus and Thymus vulgaris: nitric oxide inhibition in J774A.1 murine macrophages. *J Pharm Pharmacol*. 2004;56(2):257-263. doi:10.1211/0022357022665
39. Agbor GA, Oben JE, Ngogang JY, Xinxing C, Vinson JA. Antioxidant capacity of some herbs/spices from cameroon: a comparative study of two methods. *J Agric Food Chem*. 2005;53(17):6819-6824. doi:10.1021/jf050445c
40. Hammer KA, Carson CF, Riley TV. Antimicrobial activity of essential oils and other plant extracts. *J Appl Microbiol*. 1999;86(6):985-990. doi:10.1046/j.1365-2672.1999.00780.x
41. Sun D, Courtney HS, Beachey EH. Berberine sulfate blocks adherence of Streptococcus pyogenes to epithelial cells, fibronectin, and hexadecane. *Antimicrob Agents Chemother*. 1988;32(9):1370-1374. doi:10.1128/AAC.32.9.1370
42. Piscoya J, Rodriguez Z, Bustamante SA, Okuhama NN, Miller MJS, Sandoval M. Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: mechanisms of action of the species Uncaria guianensis. *Inflamm Res*. 2001;50(9):442-448. Accessed September 9, 2020. http://link.springer.com/10.1007/PL00000268 doi:10.1007/PL00000268
43. de Paula LCL, Fonseca F, Perazzo F, et al. Uncaria tomentosa (cat's claw) improves quality of life in patients with advanced solid tumors. *J Altern Complement Med*. 2015;21(1):22-30. Accessed September 9, 2020. http://www.liebertpub.com/doi/10.1089/acm.2014.0127 doi:10.1089/acm.2014.0127
44. Puri BK, Hakkarainen-Smith JS, Monro JA. The effect of artesunate on short-term memory in Lyme borreliosis. *Med Hypotheses*. 2017;105:4-5. Accessed February 25, 2021. http://www.ncbi.nlm.nih.gov/pubmed/28735651 doi:10.1016/j.mehy.2017.06.015
45. Sandoval M, Charbonnet RM, Okuhama NN, et al. Cat's Claw inhibits TNF production and savenges free radicals: Role in Cytoprotection. 2000 [cited 2020 Sep 8]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0891584900003270?via%3Dihub
46. Hanprasertpong N, Teekachunhatean S, Chaiwongsa R, et al. Analgesic, anti-inflammatory, and chondroprotective activities of Cryptolepis buchanani extract: In vitro and in vivo studies. Biomed Res Int. 2014 [cited 2020 Sep 9]; 2014:978582. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25247198
47. de Andrade Teles RB, Diniz TC, Costa Pinto TC, de Oliveira RG Junior, Gama E. Silva M, de Lavor EM, et al. Flavonoids as therapeutic agents in Alzheimer's and Parkinson's diseases: A systematic review of preclinical evidence. Oxid Med Cell Longev. 2018 [cited 2021 Mar 17]; 2018:7043213. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29861833
48. Lee E, Park HR, Ji ST, Lee Y, Lee J. Baicalein attenuates astroglial activation in the 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine-induced Parkinson's disease model by downregulating the activations of nuclear factor-κB, ERK, and JNK. *J Neurosci Res*. 2014;92(1):130-139. Accessed March 17, 2021. http://www.ncbi.nlm.nih.gov/pubmed/24166733 doi:10.1002/jnr.23307
49. Sowndhararajan K, Deepa P, Kim M, Park J, Kim S. Neuroprotective and cognitive enhancement potentials of baicalin: A review. Brain Sciences. 2018 [cited 2020 Sep 11]; Available from: www.mdpi.com/journal/brainsci doi:10.3390/brainsci8060104
50. Levy RM, Khokhlov A, Kopenkin S, et al. Efficacy and safety of flavocoxid, a novel therapeutic, compared with naproxen: a randomized multicenter controlled trial in subjects with osteoarthritis of the knee. *Adv Ther*. 2010;27(10):731-742. Accessed March 17, 2021. http://www.ncbi.nlm.nih.gov/pubmed/20845002 doi:10.1007/s12325-010-0064-z
51. Arjmandi BH, Ormsbee LT, Elam ML, et al. A combination of Scutellaria baicalensis and Acacia catechu extracts for short-term symptomatic relief of joint discomfort associated with osteoarthritis of the knee. *J Med Food*. 2014;17(6):707-713. Accessed March 17, 2021. http://www.ncbi.nlm.nih.gov/pubmed/24611484 doi:10.1089/jmf.2013.0010
52. Linnebur SA, Rapacchietta OC, Vejar M. Hepatotoxicity associated with chinese skullcap contained in Move Free Advanced dietary supplement: Two case reports and review of the literature. Pharmacotherapy. 2010 Jul [cited 2021 Feb 25]; 30(7):750, 258e-262e. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20586134
53. https:/www,nobelprize.org/prizes/medicine/2015/tu/facts
54. Omer B, Krebs S, Omer H, Noor TO. Steroid-sparing effect of wormwood (Artemisia absinthium) in Crohn's disease: a double-blind placebo-controlled study. *Phytomedicine*. 2007;14(2-3):87-95. Accessed February 25, 2021. http://www.ncbi.nlm.nih.gov/pubmed/17240130 doi:10.1016/j.phymed.2007.01.001
55. Weisbord SD, Soule JB, Kimmel PL. Poison on line--acute renal failure caused by oil of wormwood purchased through the Internet. *N Engl J Med*. 1997;337(12):825-827. Accessed February 25, 2021. http://www.nejm.org/doi/abs/10.1056/NEJM199709183371205 doi:10.1056/NEJM199709183371205
56. Preuss HG, Echard B, Dadgar A, et al. Effects of essential oils and monolaurin on Staphylococcus aureus: in vitro and in vivo studies. *Toxicol Mech Methods*. 2005;15(4):279-285. Accessed July 1, 2021. https://pubmed.ncbi.nlm.nih.gov/20021093/ doi:10.1080/15376520590968833
57. Lantos PM, Shapiro ED, Auwaerter PG, et al. Unorthodox alternative therapies marketed to treat Lyme disease. *Clin Infect Dis*. 2015;60(12):1776-1782. Accessed February 25, 2021. http://www.ncbi.nlm.nih.gov/pubmed/25852124 doi:10.1093/cid/civ186