

The Unique Challenges of Lyme Disease and a Multi-Pronged Strategy to Address Them

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References

1. Balmelli T, Piffaretti JC. Association between different clinical manifestations of Lyme disease and different species of *Borrelia burgdorferi* sensu lato. *Res Microbiol*. 1995 May;146(4):329-40.
2. Rudenko N, et al. Updates on *Borrelia burgdorferi* sensu lato complex with respect to public health. *Ticks Tick Borne Dis*. 2011 Sep;2(3):123-8.
3. Lantos PM, Wormser GP. Chronic coinfections in patients diagnosed with chronic lyme disease: a systematic review. *Am J Med*. 2014 Nov;127(11):1105-10.
4. Mitchell PD, et al. Immunoserologic evidence of coinfection with *Borrelia burgdorferi*, *Babesia microti*, and human granulocytic Ehrlichia species in residents of Wisconsin and Minnesota. *J Clin Microbiol*. 1996 Mar;34(3):724-7.
5. Diuk-Wasser MA, et al. Coinfection by Ixodes Tick-Borne Pathogens: Ecological, Epidemiological, and Clinical Consequences. *Trends Parasitol*. 2016 Jan;32(1):30-42.
6. Zajkowska J, et al. [Atypical forms of *Borrelia burgdorferi*--clinical consequences]. *Pol Merkur Lekarski*. 2005 Jan;18(103):115-9.
7. Singh SK, Girschick HJ. Molecular survival strategies of the Lyme disease spirochete *Borrelia burgdorferi*. *Lancet Infect Dis*. 2004 Sep;4(9):575-83.
8. Sapi E, et al Characterization of biofilm formation by *Borrelia burgdorferi* in vitro. *PLoS One*. 2012 Oct 24;7(10):e48277.
9. Miklossy J, et al. Persisting atypical and cystic forms of *Borrelia burgdorferi* and local inflammation in Lyme neuroborreliosis. *J Neuroinflammation*. 2008 Sep 25;5:40.
10. Steere AC, et al. Prospective study of serologic tests for lyme disease. *Clin Infect Dis*. 2008 Jul 15;47(2):188-95.
11. Klayman DL. Qinghaosu (artemisinin): an antimalarial drug from China. *Science*. 1985 May 31;228(4703):1049-55.
12. Tariq A, et al. Ethnomedicines and anti-parasitic activities of Pakistani medicinal plants against Plasmodia and Leishmania parasites. *Ann Clin Microbiol Antimicrob*. 2016 Sep 20;15(1):52.
13. White NJ, et al. A Brief History of Qinghaosu. *Trends Parasitol*. 2015 Dec;31(12):607-610.
14. Bilia AR, et al. Essential Oil of *Artemisia annua* L.: An Extraordinary Component with Numerous Antimicrobial Properties. *Evid Based Complement Alternat Med*. 2014;2014:159819.
15. Efferth T, et al. The antiviral activities of artemisinin and artesunate. *Clin Infect Dis*. 2008 Sep 15;47(6):804-11.
16. D'Angelo JG, et al. Artemisinin derivatives inhibit *Toxoplasma gondii* in vitro at multiple steps in the lytic cycle. *J Antimicrob Chemother*. 2009 Jan;63(1):146-50.
17. Loo CS, et al. Artemisinin and its derivatives in treating protozoan infections beyond malaria. *Pharmacol Res*. 2017 Mar;117:192-217.
18. Goo YK, et al. Artesunate, a potential drug for treatment of *Babesia* infection. *Parasitol Int*. 2010 Sep;59(3):481-6.
19. Goswami S, et al. Anti-*Helicobacter pylori* potential of artemisinin and its derivatives. *Antimicrob Agents Chemother*. 2012 Sep;56(9):4594-607.
20. Bilia AR, et al. Essential Oil of *Artemisia annua* L.: An Extraordinary Component with Numerous Antimicrobial Properties. *Evid Based Complement Alternat Med*. 2014;2014:159819.
21. Militaru D, et al. In vitro evaluation of the potential antibacterial effect of artemisinin on *Campylobacter jejuni*. *Rom Biotech Let*. 2015 Mar 1;20(2):10221-7.
22. Engberg RM, et al. The effect of *Artemisia annua* on broiler performance, on intestinal microbiota and on the course of a *Clostridium perfringens* infection applying a necrotic enteritis disease model. *Avian Pathology*. 2012 Aug 1;41(4):369-76.
23. De Cremer K, et al. Artemisinins, new miconazole potentiators resulting in increased activity against *Candida albicans* biofilms. *Antimicrob Agents Chemother*. 2015 Jan;59(1):421-6.
24. Sisto F, et al. In vitro activity of artemisone and artemisinin derivatives against extracellular and intracellular *Helicobacter pylori*. *Int J Antimicrob Agents*. 2016 Jul;48(1):101-5.
25. Puri BK, et al. The effect of artesunate on short-term memory in Lyme borreliosis. *Med Hypotheses*. 2017 Aug;105:4-5.
26. Avula B, et al. Simultaneous identification by liquid chromatography of benzethonium chloride, methyl paraben and triclosan in commercial products labeled as grapefruit seed extract. *Pharmazie*. 2007 Aug;62(8):593-596.
27. Sugimoto N, et al. [Survey of synthetic disinfectants in grapefruit seed extract and its compounded products]. *Shokuhin Eiseigaku Zasshi*. 2008 Feb;49(1):56-62.
28. Brorson O, Brorson SH. Grapefruit seed extract is a powerful in vitro agent against motile and cystic forms of *Borrelia burgdorferi* sensu lato. *Infection*. 2007 Jun 1;35(3):206.
29. Goc A, Rath M. The anti-borreliae efficacy of phytochemicals and micronutrients: an update. *Ther Adv Infect Dis*. 2016 Jun;3(3-4):75-82.

30. Ionescu G, et al. Oral citrus seed extract in atopic eczema: In vitro and in vivo studies on intestinal microflora. *J Orthomolecular Med.* 1990;5:155-7.
31. Wurm M, et al. Pentacyclic oxindole alkaloids from *Uncaria tomentosa* induce human endothelial cells to release a lymphocyte-proliferation-regulating factor. *Planta Med.* 1998 Dec;64(8):701-4.
32. Domingues A, et al. *Uncaria tomentosa* aqueous-ethanol extract triggers an immunomodulation toward a Th2 cytokine profile. *Phytother Res.* 2011 Aug;25(8):1229-35.
33. Mur E, et al. Randomized double blind trial of an extract from the pentacyclic alkaloid-chemotype of *uncaria tomentosa* for the treatment of rheumatoid arthritis. *J Rheumatol.* 2002 Apr;29(4):678-81.
34. Piscocya J, et al. 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 Sep;50(9):442-8.
35. Gonçalves C, Dinis T, Batista MT. Antioxidant properties of proanthocyanidins of *Uncaria tomentosa* bark decoction: a mechanism for anti-inflammatory activity. *Phytochemistry.* 2005 Jan;66(1):89-98.
36. Sandoval M, et al. Cat's claw inhibits TNF α production and scavenges free radicals: role in cytoprotection. *Free Radic Biol Med.* 2000 Jul 1;29(1):71-8.
37. Mohamed AF, et al. Effects of *Uncaria tomentosa* total alkaloid and its components on experimental amnesia in mice: elucidation using the passive avoidance test. *J Pharm Pharmacol.* 2000 Dec;52(12):1553-61.
38. Lee SC, et al. Effects of repeated administration of *Uncaria hooks* on the acquisition and central neuronal activities in ethanol-treated mice. *J Ethnopharmacol.* 2004 Sep;94(1):123-8.
39. Santo GD, et al. Protective effect of *Uncaria tomentosa* extract against oxidative stress and genotoxicity induced by glyphosate-Roundup $\text{\textcircled{R}}$ using zebrafish (*Danio rerio*) as a model. *Environ Sci Pollut Res Int.* 2018 Feb 13.
40. Siqueiros-Cendón T, et al. Immunomodulatory effects of lactoferrin. *Acta Pharmacol Sin.* 2014 May;35(5):557-66.
41. Moreno-Expósito L, et al. Multifunctional capacity and therapeutic potential of lactoferrin. *Life Sci.* 2018 Feb 15;195:61-64.
42. Singh PK, et al. A component of innate immunity prevents bacterial biofilm development. *Nature.* 2002 May;417(6888):552.
43. Haenel D, Sapi E. Significant antimicrobial effects of lactoferrin on *Borrelia burgdorferi* biofilm. University of New Haven. Poster.
44. Ikadai H, et al. Inhibitory effect of lactoferrin on in vitro growth of *Babesia caballi*. *Am J Trop Med Hyg.* 2005 Oct;73(4):710-2.
45. Butler T. The Jarisch-Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. *Am J Trop Med Hyg.* 2017 Jan 11;96(1):46-52.
46. Maloy AL, Black RD, Segurola RJ Jr. Lyme disease complicated by the Jarisch-Herxheimer reaction. *J Emerg Med.* 1998 May-Jun;16(3):437-8.
47. Webster G, et al. Jarisch-Herxheimer reaction associated with ciprofloxacin administration for tick-borne relapsing fever. *Pediatr Infect Dis J.* 2002 Jun;21(6):571-3.
48. Zhang GH, et al. Neutralization of endotoxin in vitro and in vivo by a human lactoferrin-derived peptide. *Infect Immun.* 1999 Mar;67(3):1353-8.
49. Ellass-Rochard E, et al. Lactoferrin inhibits the endotoxin interaction with CD14 by competition with the lipopolysaccharide-binding protein. *Infect Immun.* 1998 Feb;66(2):486-91.
50. Mattsby-Baltzer I, et al. Lactoferrin or a fragment thereof inhibits the endotoxin-induced interleukin-6 response in human monocytic cells. *Pediatr Res.* 1996 Aug;40(2):257-62.
51. Drago-Serrano ME, et al. Lactoferrin: Balancing Ups and Downs of Inflammation Due to Microbial Infections. *Int J Mol Sci.* 2017 Mar 1;18(3).
52. Kruzel ML, et al. Lactoferrin protects gut mucosal integrity during endotoxemia induced by lipopolysaccharide in mice. *Inflammation.* 2000 Feb;24(1):33-44.
53. Lee WJ, et al. The protective effects of lactoferrin feeding against endotoxin lethal shock in germfree piglets. *Infect Immun.* 1998 Apr;66(4):1421-6.
54. Gerente C, et al. Application of chitosan for the removal of metals from wastewaters by adsorption—mechanisms and models review. *Crit Rev Environ Sci Tech.* 2007 Jan 1;37(1):41-127.
55. Dehghani MH, et al. Adsorptive removal of endocrine disrupting bisphenol A from aqueous solution using chitosan. *J Environ Chem Eng.* 2016 Sep 30;4(3):2647-55.
56. Salim CJ, Liu H, Kennedy JF. Comparative study of the adsorption on chitosan beads of phthalate esters and their degradation products. *Carbo Polymers.* 2010 Jul 7;81(3):640-4.
57. Dehghani MH, et al. Adsorptive removal of endocrine disrupting bisphenol A from aqueous solution using chitosan. *J Environ Chem Eng.* 2016 Sep 30;4(3):2647-55.
58. Bornet A, Teissedre PL. Chitosan, chitin-glucan and chitin effects on minerals (iron, lead, cadmium) and organic (ochratoxin A) contaminants in wines. *Euro Food Res Tech.* 2008 Feb 1;226(4):681-9.
59. Quintela S, et al. Ochratoxin A removal from red wine by several oenological fining agents: bentonite, egg albumin, allergen-free adsorbents, chitin and chitosan. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2012;29(7):1168-74.
60. Guan B, et al. Removal of Mn (II) and Zn (II) ions from flue gas desulfurization wastewater with water-soluble chitosan. *Sep*

Purif Tech. 2009 Mar 12;65(3):269-74.

61. Wu ZB, Ni WM, Guan BH. Application of chitosan as flocculant for coprecipitation of Mn (II) and suspended solids from dual-alkali FGD regenerating process. *J Haz Mat.* 2008 Apr 1;152(2):757-64.
62. Troxell B, et al. Manganese and zinc regulate virulence determinants in *Borrelia burgdorferi*. *Infect Immun.* 2013 Aug;81(8):2743-52.
63. Aguirre JD, et al. A manganese-rich environment supports superoxide dismutase activity in a Lyme disease pathogen, *Borrelia burgdorferi*. *J Biol Chem.* 2013 Mar 22;288(12):8468-78.
64. Pu Y, et al. In vitro damage of *Candida albicans* biofilms by chitosan. *Exp Ther Med.* 2014 Sep;8(3):929-934.
65. Chávez de Paz LE, et al. Antimicrobial effect of chitosan nanoparticles on streptococcus mutans biofilms. *Appl Environ Microbiol.* 2011 Jun;77(11):3892-5.
66. Davydova VN, et al. Interaction of bacterial endotoxins with chitosan. Effect of endotoxin structure, chitosan molecular mass, and ionic strength of the solution on the formation of the complex. *Biochemistry (Mosc).* 2000 Sep;65(9):1082-90.
67. Solov'eva T, et al. Marine compounds with therapeutic potential in gram-negative sepsis. *Mar Drugs.* 2013 Jun 19;11(6):2216-29.
68. Hines SW. Nano-Particle Chitosan: New Hope for Lyme-Related Herxheimer Symptoms. *Focus.* 2007 July:9-10.
69. Lee HW, et al. Chitosan oligosaccharides, dp 2-8, have prebiotic effect on the *Bifidobacterium bifidum* and *Lactobacillus* sp. *Anaerobe.* 2002 Dec;8(6):319-24.
70. Cani PD, et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia.* 2007 Nov 1;50(11):2374-83.
71. Roselli M, et al. Probiotic bacteria *Bifidobacterium animalis* MB5 and *Lactobacillus rhamnosus* GG protect intestinal Caco-2 cells from the inflammation-associated response induced by enterotoxigenic *Escherichia coli* K88. *Brit J Nutr.* 2006 Jun;95(6):1177-84.
72. Peacock BN, et al. New insights into Lyme disease. *Redox Biol.* 2015 Aug;5:66-70.
73. Sambri V, Cevenini R. Incorporation of cysteine by *Borrelia burgdorferi* and *Borrelia hermsii*. *Can J Microbiol.* 1992 Oct;38(10):1016-21.
74. Nicolson GL, et al. Lipid replacement therapy with a glycopospholipid formulation with NADH and CoQ10 significantly reduces fatigue in intractable chronic fatiguing illnesses and chronic Lyme disease patients. *Int J Clin Med.* 2012 May 29;3(03):163.
75. Nicolson GL. Lipid replacement/antioxidant therapy as an adjunct supplement to reduce the adverse effects of cancer therapy and restore mitochondrial function. *Pathol Oncol Res.* 2005;11(3):139-44.
76. Agadjanyan M, et al. Nutritional supplement (NT Factor™) restores mitochondrial function and reduces moderately severe fatigue in aged subjects. *J Chronic Fat Syn.* 2003;11(3):23-36.