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PANS/PANDAS

DISCLOSURES

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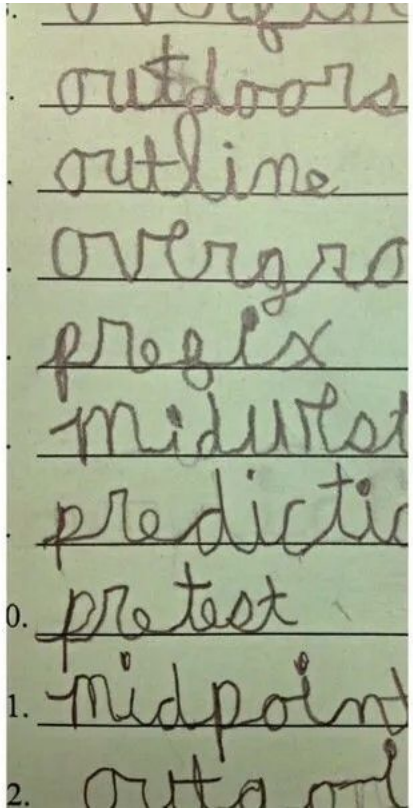
Overview of PANS/PANDAS

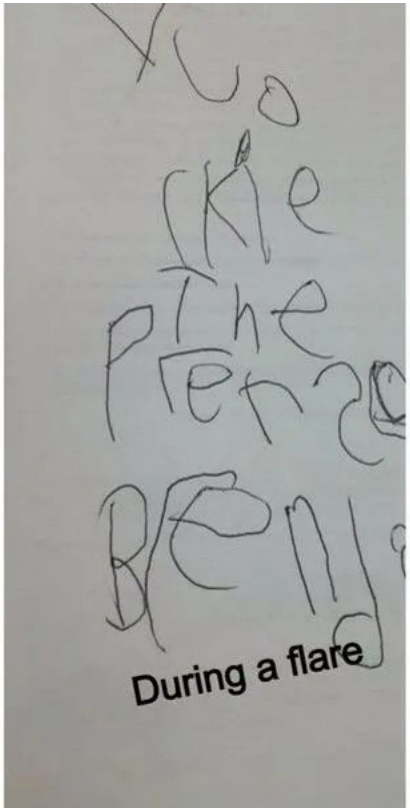
- Autoimmune encephalopathy/Inflammation of the basal ganglia

- It is relapsing/remitting.
  - When the inflammation/trigger is addressed they get better
  - If a trigger recurs, the symptoms come back.

PANS

- Consider whenever symptoms of OCD, eating restrictions or tics start suddenly
- And are accompanied by:
  - other emotional and behavioral changes
  - frequent urination
  - motor abnormalities and/or handwriting changes.
- **The Big 3: major symptoms are OCD, separation anxiety, and anorexia.**
- **90% of people have a change in handwriting.**





History of PANS/PANDAS

- 1998: Dr Susan Swedo publishes "PANDAS : The Clinical Description of the First 50 cases" in *Psychiatry*.
  - She observed that streptococcus infections were causing neuropsychiatric symptoms
- 2010: NIMH 2010 meeting resulted in a new term, Pediatric Autoimmune Neuropsychiatric Syndrome (PANS)
  - widened the potential triggers beyond strep infections.

Basal Ganglia Inflammation

- Motor function: Tics, Choreiform (dancy/rhythmic) movements
- Mood and emotion: OCD, Emotional Lability, Anxiety
- Behaviors: Clinginess, Tantrums, Rage
- Procedural learning: poor handwriting, clumsy
- Cognition: Slow processing, memory issues
- Sensory issues: Sensitive to sound, lights, smells, textures, etc

TILT: Total Immune Lack of Tolerance

- This is a disorder of immune system activation
- After addressing the acute illness, we need to lower the burden on the immune system so that they don't have a future flare with every little exposure.
- Consider viral loads, mycotoxins, nutrient deficiencies, toxicities, poor lifestyle factors, immune system imbalances, allergies, food intolerances, gluten, etc.

TREATMENT STRATEGY

- **Put out the Fire**: Anti-inflammatory
- **Identify Root Cause**: There may be multiple triggers
- **Keep the Fire Down**: Immune Modulation
  - Pathogens do NOT need to be present for symptoms to occur.
  - The autoimmune response may occur without the presence of the initial trigger.

Basic Treatment Approach

- Foundational Support (Nutritional, Lifestyle, FRAT testing, etc)
- **Anti-Inflammatories**
- **Immune Modulators (BALANCE)**
- **Detox and Drainage Support**
- Address Root Causes and Triggers
  - **Mycoplasma, Lyme and Coinfections (Bartonella, Babesia)**
  - Mold and Mycotoxins
  - Candida/Yeast
  - Allergies
  - Stress /Trauma
- Mast Cell Support
  - Quercetin/ Luteolin
  - Antihistamines /H2 Blockers
  - Bromelain or Digestive Enzymes
- OCD Specific Supplementation
- Referrals as Indicated (cardiology, neuro, psych, cognitive behavioral therapy, etc)
- EXTREME cases: refer for IVIG or Plasmapheresis

Anti-Inflammatories and Immune Modulators

Anti-Inflammatories

- Curcumin (ie NM Avea)
- Fish Oil (EPA)
- Resolvins/SPM's
- Sulfurophane
- Ibuprofen/Naproxen/Steroid Tapers
- Takuna (perhaps AntiMicrobial/ empiric antiviral properties)
- Samento/ TOA-free cat's claw (Also AntiMicrobial)
- Banderol (*Otoba parvifolia* (bark)) (Also AntiMicrobial)
- Cumanda/ *Campsiandra angustifolia* (Also Antimicrobial)

Immune Modulators

- Probiotics
- Digestive Enzymes/Bromelain
- Vitamin D
- LDN
- Samento (Also AntiMicrobial)
- Houttynia (Also AntiMicrobial)
- Baikal Skullcap (Also AntiMicrobial)

Ibuprofen/Naproxen

- Ibuprofen and naproxen impair proton gradient in electron transfer chain
- Therefore, use nutraceuticals whenever possible

Wallace KB. Drug-induced mitochondrial neuropathy in children: a conceptual framework for critical windows of development. J Child Neurol. 2014 Sep;29(9):1241-8. doi: 10.1177/0883073814538510. Epub 2014 Jul 9. PMID: 25008905.

Takuna (*Cecropia strigosa* (bark))

- Feldene, a prescription anti-inflammatory, was only 38.5% as effective as Takuna for treating inflammation.
- **Takuna was more than twice as effective as Feldene**.
- Takuna is superior to Feldene for treating inflammation.

Allende, S. (2007). Determination of the possible Anti-inflammatory effect of the product named TAKUNA (liquid), produced by the Laboratories of NutraMedix, LLC, Florida. University of Guayaquil Faculty of Chemical Sciences, Guayaquil, Ecuador.

Curcumin

The anti-arthritic activity of turmeric (rich in curcuminoids) exceeded that of ginger and indomethacin (a non-steroidal anti-inflammatory drug).

- The percentage of disease recovery was greater with turmeric compared with ginger and indomethacin

Curcumin reduces inflammatory chemicals: NFKB, Il-8, IL-1B, IL-6

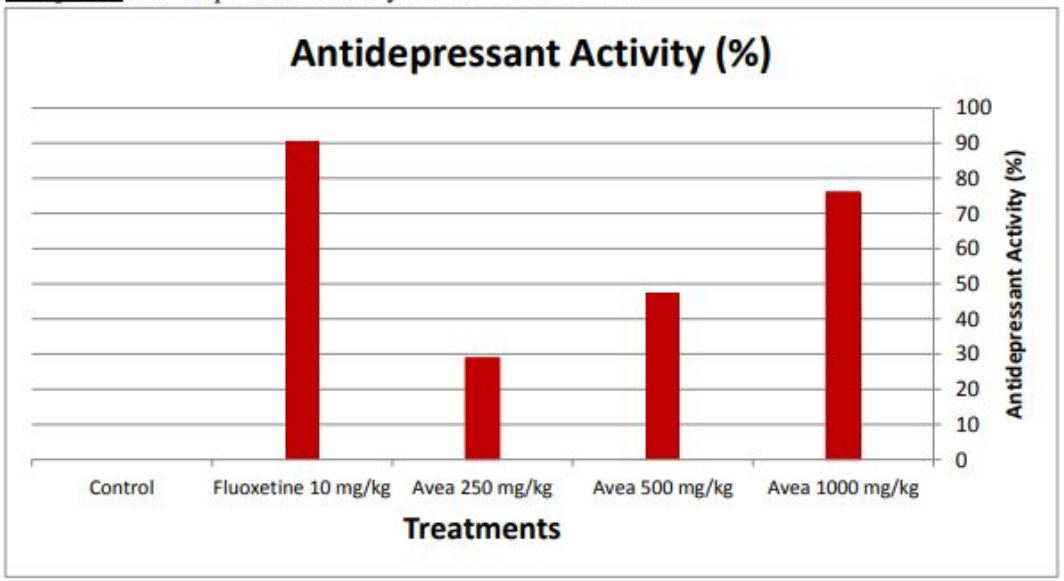
- Ramadan G, Al-Kahtani MA, El-Sayed WM. Anti-inflammatory and anti-oxidant properties of Curcuma longa (turmeric) versus Zingiber officinale (ginger) rhizomes in rat adjuvant-induced arthritis. Inflammation. 2011 Aug;34(4):291-301. doi: 10.1007/s10753-010-9278-0. PMID: 21120596.

Avea = Liquid Curcumin

Table #3: Antidepressant Activity (%)

Doses	Activity (%)
Control	-
Fluoxetine 10 mg/kg	90.66
AVEA 250 mg/kg	28.92
AVEA 500 mg/kg	47.63
AVEA 1000 mg/kg	76.07

Graph #1: Antidepressant activity in rats with **AVEA**.



- AVEA: Anti-depressant Effect Experiment Administered at Cayetano Heredia University of Peru Study Completed: November 6th, 2018

Detox and Drainage Support

Burbur-Pinella

- **Burbur**
- *Desmodium molliculum* (leaf)

- **Pinella**
- *Pimpinella spp.* (stem)

Burbur Pinella (in vivo; rats)

- **Supports liver detoxification** (b,p) (Gordillo et al., 2019; Asadollahpoor et al., 2017)
- **Supports kidney detoxification** (p) (Amina et al., 2016)
- **Supports colon detoxification** (p) (Kreydiyyeh et al., 2004)
- **Detoxification can help with neurological support** (p)
- **Anticonvulsant and neuroprotective effects** (Karimdadeh, 2012; Pourgholami et al., 1999)

Burbur Pinella

- May be helpful for **Herxheimer reactions**
  - new or worsening symptoms from the toxins released by dying microbes.

Herxheimer Reactions

- **Burbur/Pinella** (for lymphatic and glymphatic support/Herxheimer support and more!) **20 drops twice daily**. Add extra doses for any new or worsening symptoms.
- This is basic support for ALL treatment protocols. This may be used with ANY microbial treatment regimen, whether using prescription antimicrobials or herbal supplements or adjunctive therapies. This may be begun before initiating therapy if the patient is sensitive, or it may be begun with therapy.
- **May put 2-4 full dropperfuls in a bottle of water and sip on throughout the day.** This is great for kids to take to school!
- Take one dropperful every 10 minutes for up to an hour for any new or worsening symptom during treatment. (**6 droppersful in glass and drink over an hour**)
- May be used with additional support products such as curcumin, chlorella, glutathione, etc.

Address Root Causes and Triggers

Could It Be Lyme?

- Neurological and psychiatric symptoms as well as complex chronic illnesses frequently involve persistent microbes, including Lyme disease.
- **Borrelia, the agent that causes Lyme disease, can "cause immune and metabolic effects that result in a gradually developing spectrum of neuropsychiatric symptoms usually presenting with significant comorbidity which may include developmental disorders, autism spectrum disorders**, schizoaffective disorders, bipolar disorder, depression, anxiety disorders (panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, and intrusive symptoms), eating disorder, decreased libido, sleep disorder, addiction, opioid addiction, cognitive impairments, dementia, seizure disorders, suicide, violence, anhedonia, depersonalization, dissociative episodes, derealization, and other impairments"

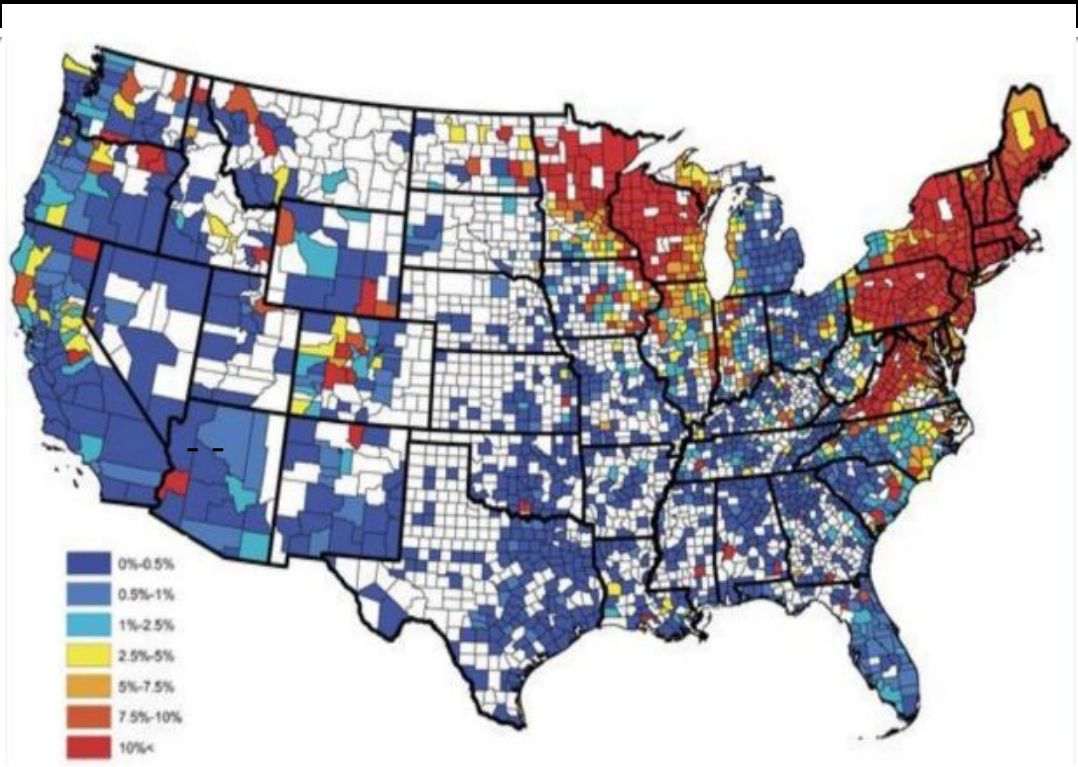
- Bransfield R. Neuropsychiatric lyme borreliosis: an overview with a focus on a specialty psychiatrist's clinical practice. *Healthcare.* (2018) 6:104. 10.3390/healthcare6030104

Lyme is an Epidemic

Lyme Disease– Reported to be the most common vector-borne infectious disease in the Northern United States

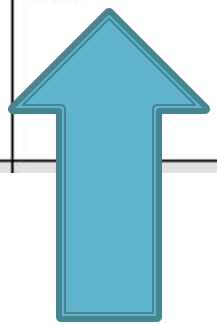
"May 11, 2017 - As the rate of **Lyme disease grows rapidly across the United States,** new research offers veterinarians a forecasting map that tells them which parts of the country are most at risk of Lyme disease infections in dogs, which could also help track and predict Lyme disease in people."

Source: InfectionControlToday.com



Lyme and Coinfections Chart

Coinfections	Vector	Causative Agent	Endemic Area	Symptoms
Lyme Disease (also called STARI or Masters' Disease)	Deer Tick Pacific Black-legged Tick Lone Star Tick	*Borrelia burgdorferi* *Borrelia lonestari* *Other Borrelia?*	Throughout US	Off season "flu" Rash (bull's-eye or other) Constitutional symptoms Musculoskeletal symptoms Wide range of neurologic symptoms, including Bell's Palsy



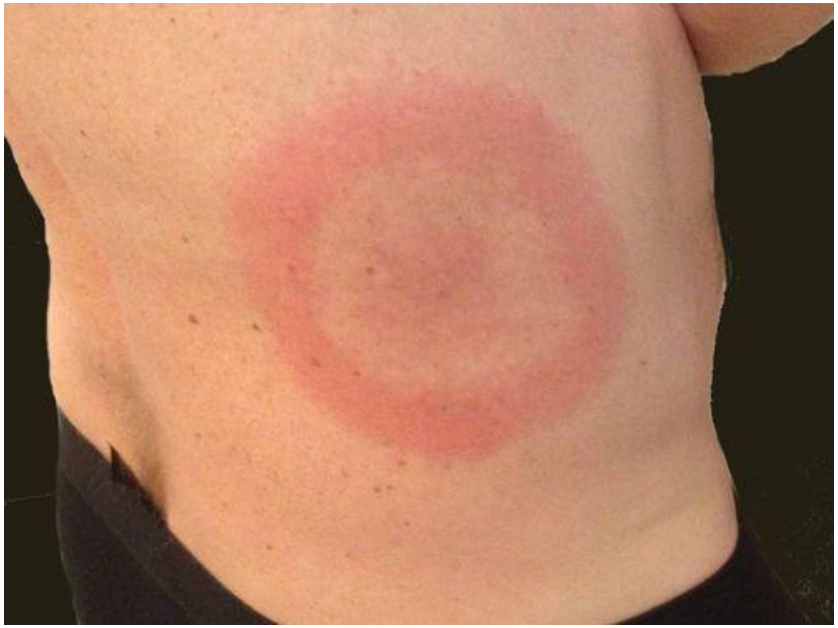
- https://www.lymedisease.org/wp-content/uploads/2014/08/Screen-Shot-2014-08-26-at-5.02.12-PM.png, Accessed on 7/20/23

LYME STAGES OF DISEASE

- Stage I: Early-stage disease
  - erythema migrans rash
  - flu-like symptoms: temperature, chills and **neck stiffness, joint and muscle pain, swollen lymph glands, fatigue.**
- Stage II: Early disseminated disease
  - Inflammation: joint pain and swelling
  - Neurological: e.g. **tingling, numbness, neuropathy, memory problems, difficulty concentrating.**
  - The triad of meningitis, cranial neuritis and polyradiculitis is classic of neurological involvement
  - Cardiac, e.g., myocarditis, pericarditis, bundle branch block, heart rhythm disturbances
- Stage III: Late disseminated disease
  - Large-joint arthritis (over 50% of cases)
  - **Encephalopathy,** peripheral neuropathy, aphasia, hemiplegia (rarely), seizures
  - **Anxiety, psychosis and hallucinations**
- https://aonm.org/aonm-lyme-disease-faqs/

DIAGNOSING LYME

- **It is a clinical diagnosis** supported by appropriate testing (likelihood of a false negative is high)
- Only 17% recall a tick bite
- Only 36% recall a rash
- **55% with chronic Lyme have negative blood tests**



Root Cause Combo

- Antibiotics
  - Multiple may be required
  - Side effects
- Herbs
  - Safer
  - Simpler
  - Less expensive
  - Require less monitoring
  - Cover more microbes
  - Side benefits

GlucoMedix

Stevia leaf
(*Stevia rebaudiana)*

Samento Cat's Claw bark

(*Uncaria tomentosa*)

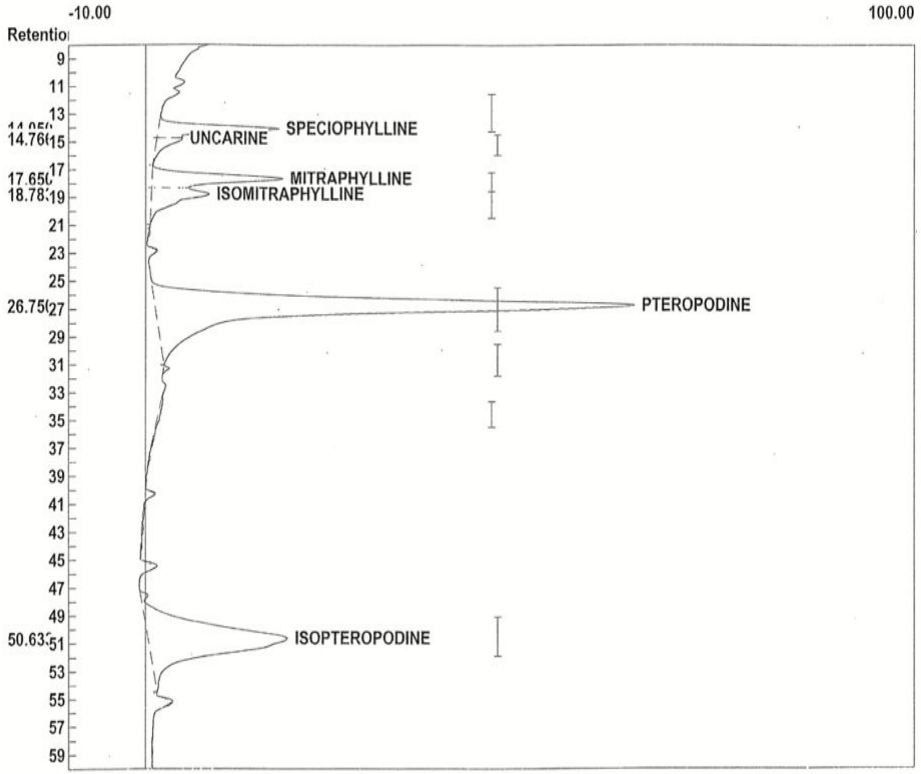
Samento

- Uña de gato
- Cat's Claw
- *Uncaria tomentosa* (bark)

Why Samento is Unique (pentacyclic chemotype)

Oxindole Alkaloids:
-Tetracyclic Oxindole Alkaloids (TOAs) – rhynchophylline, isorhynchophylline

-Pentacyclic Oxindole Alkaloids (POAs) – speciophylline, uncarine F, mitrapylline, isomitraphylline, pteropotidine, isopteropodine



14.050	SPECIOPHYLLINE	554.86	5.98	0.03 %
14.766	UNCARINE	134.78	1.45	0.02 %
17.650	MITRAPHYLLINE	746.88	8.05	0.04 %
18.783	ISOMITRAPHYLLINE	455.67	4.91	0.27 %
26.750	PTEROPODINE	4887.40	52.68	0.37 %
0.000	RHYNCHOPHYLLIN	0.00	0.00	0.00 %
0.000	ISORHYNCHOPHYLLIN	0.00	0.00	0.00 %
50.633	ISOPTEROPODINE	2498.73	26.93	0.22 %
		9278.31	100.00	0.95

No TOAs!

Why the Pentacyclic Chemotype (POA) Matters

- TOA's are immune stimulating
- POA's are immune modulating
- TOA's are antagonistic to POA's
- Therefore, when TOAs are present, cat's claw can only act as an immune *stimulator*.
- When TOAs are absent, cat's claw can act as an immune *modulator*
  - ↑ immunity in immune deficiency
  - ↓ Immunity in immune excess

Recognition of Samento

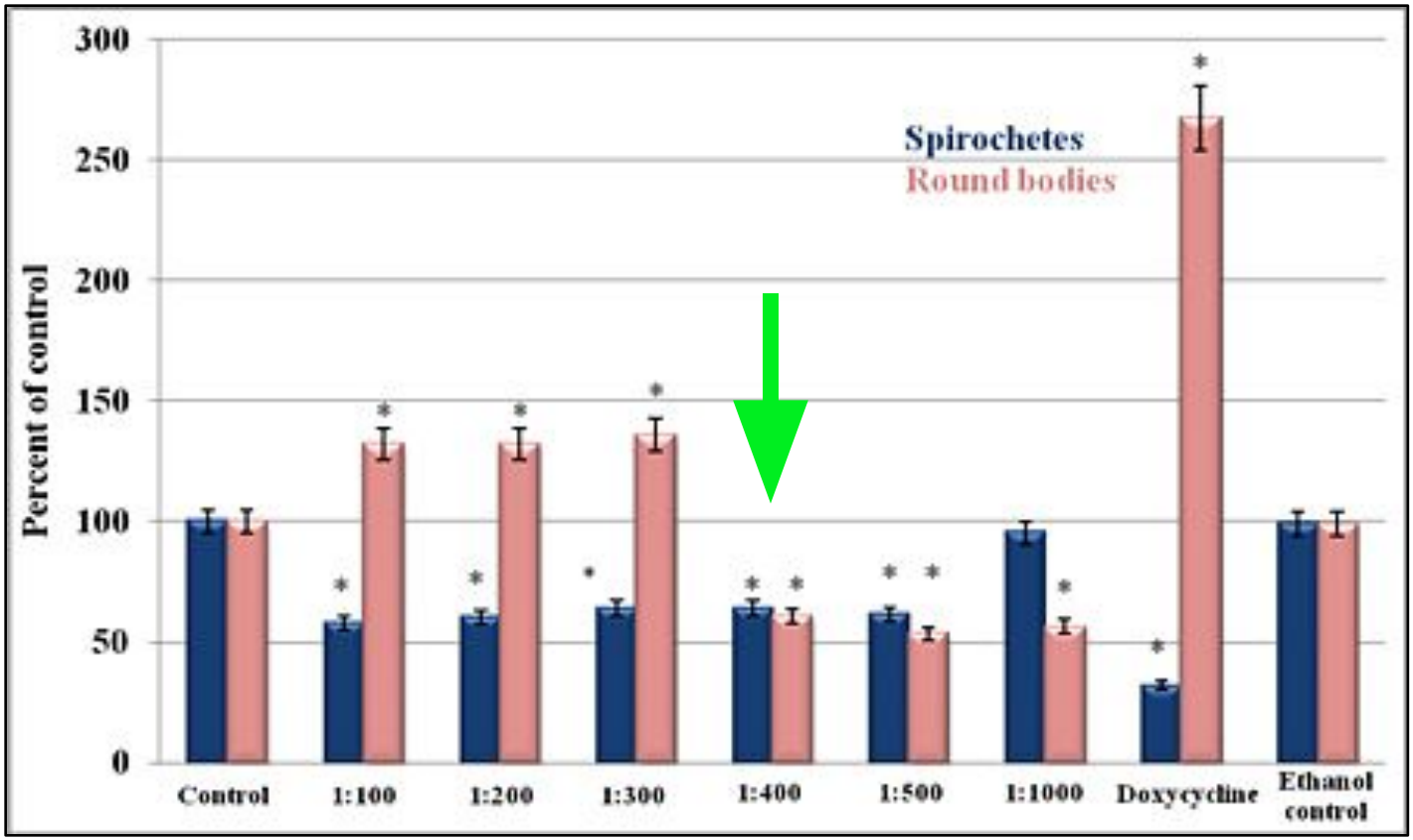
- Approved as a medicine in Ecuador in 2004.
  - **immune system modulator**
  - **anti-inflammatory**
  - **antimicrobial**
    - Antiviral
    - Antibacterial

Samento for Lyme Disease

- **Pilot Study: Effective Treatment of Lyme Borreliosis with Pentacyclic Alkaloid Uncaria tomentosa (TOA-free Cat's Claw)**, Dallas, Texas, 2003.
- 6-month study in 28 patients with advanced, laboratory-confirmed (IgG, IgM) *Borrelia burgdorferi* infection
- Compared treatment with NutraMedix TOA-free Cat's Claw to standard antibiotic treatment
- More patients in the Samento group experienced improvements in all symptoms, including neurological symptoms and fatigue ($p<0.05$)
- The antibiotic group (n=14)
  - 3 improved slightly
  - 3 got worse
  - 8unchanged
- The experimental group (n=14) was treated with Samento
  - **100% of patients experienced marked clinical improvement**
  - **85% were seronegative for Lyme borreliosis at end of study**

Samento vs Doxycycline

(Datar et al., 2010)



SAMENTO

Spirochetes – blue

Round bodies – tan

Samento as Inflammatory

- Samento helps to lower **NF-kappaB**, which is responsible for increasing inflammatory cytokines (Sandoval-Chacón et al., 1998)
- Mitraphylline (POA) helps to lower other specific **inflammatory cytokines including IL-6, IL-1beta and TNF-alpha** (Lemaire et al., 1999; Sandoval et al., 2000; Rojas-Duran et al., 1999; Allen-Hall et al., 2007)
- Samento was **86% as effective as piroxicam/Feldene** (NSAID) in mice (University of Guayaquil, 2005)

Samento for Inflammation

- **“Prophylaxis and Treatment of Inflammation with Pentacyclic Chemotype of Uncaria tomentosa”.** Published in “Integrative Medicine” July 2023.

- **The highest dose of Samento had an 85% benefit compared to 90% with methotrexate for treatment of inflammation in a rheumatoid arthritis model in rats.**

- The results were statistically significant in all groups.

Villegas Vilchez. Prophylaxis and Treatment of Inflammation with U. tomentosa Integrative Medicine. Vol. 22, No. 3. July 2023.

Samento Prevents Inflammation

- **“Prophylaxis and Treatment of Inflammation with Pentacyclic Chemotype of Uncaria tomentosa”.** Published in “Integrative Medicine” **July 2023**.
- A potent irritant (carageenan) was given to rats.
- Prior treatment was given, with either Samento or Naproxen, to prevent the inflammatory response.
- **The highest dose of Samento had a 74% benefit compared to 97% with naproxen for prevention of inflammation.**
- The results were statistically significant in all groups.

(Villegas Vilchez, 2023)

Samento in Rheumatoid Arthritis

- Mur, E., Hartig, F., Eibl, G., & Schirmer, M. (2002). **Randomized double-blind trial of an extract from the pentacyclic alkaloid-chemotype of *Uncaria tomentosa* for the treatment of rheumatoid arthritis**. *The Journal of Rheumatology*, 29(4), 678-681.
- 52-week study with 40 patients undergoing sulfasalazine or hydroxychloroquine treatment
  - First phase (24 weeks): patients were randomly assigned to Cat's Claw or placebo
  - Second phase (28 weeks): all patients received Cat's Claw
- Phase 1 resulted in a reduction in the number of painful joints (53.2% vs. 24.1%)
- Phase 2 resulted in a decrease in the number of painful joints and swollen joints

Additional Benefits of Samento

- **Blood Sugar Support** (in vivo, mice)
  - **Type 2 – insulin sensitivity, blood glucose** (Araujo et al., 2018; Arauj et al., 2017)
  - **Type 1 – prevention?** (Domingues et al., 2011)

- **Neurological Support** (in vivo; in vitro)
  - **Memory** (Mohamed et al., 2000)
  - **Beta-amyloid protein, tau protein tangles** (Snow et al., 2019; Frackowiack et al., 2006)

- **Antioxidant Support** (in vitro)

(Sandoval et al., 2002; Batiha et al., 2020)

- **Cardiovascular Support** (in vitro)

(Horie et al., 1992)

Stevia

- Stevia
- Sweetleaf
- *Stevia rebaudiana* (leaf)

Stevia: Established Antimicrobial Activity

- Antiviral
- Antibacterial
  - *Borrelia burgdorferi* in Lyme disease
    - Spirochetes
    - Round bodies
    - Biofilms

Ghosh S, Subudhi E, Nayak S: Antimicrobial assay of Stevia rebaudiana Bertoni leaf extracts against 10 pathogens plant materials and microorganisms determination of minimum inhibitory concentration (MIC). Int J Integrative Biology 2, 27–31 (2008)

Mohammadi-Sichani, M: Effect of different extracts of Stevia rebaudiana leaves on Streptococcus mutans growth. J Med Plants Res 6, 4731–4734 (2012)

Jayaraman S, Manoharan MS: In-vitro antimicrobial and antitumor activities of Stevia rebaudiana (Asteraceae) Leaf Extracts 7, 1143–1149 (2008)

Siddique AB, Rahman SMM, Hossain MA, Rashid MA: Phytochemical screening and comparative antimicrobial potential of different extracts of Stevia rebaudiana Bertoni leaves. Asian Pacific J Trop Dis 4, 275–280 (2014)

Puri M, Sharma D: Antibacterial activity of stevioside towards food-borne pathogenic bacteria. Eng Life Sci 11, 326–329 (2011)

Takahashi, K., Matsuda, M., Ohashi, K., Taniguchi, K., Nakagomi, O., Abe, Y., Mori, S., Sato, N., Okutani, K., & Shigeta, S. (2001). Analysis of anti-rotavirus activity of extract from Stevia rebaudiana. *Antiviral research*, *49*(1), 15–24. https://doi.org/10.1016/s0166-3542(00)00134-0

(Theophilus et al., 2015)

Stevia: Brand Matters

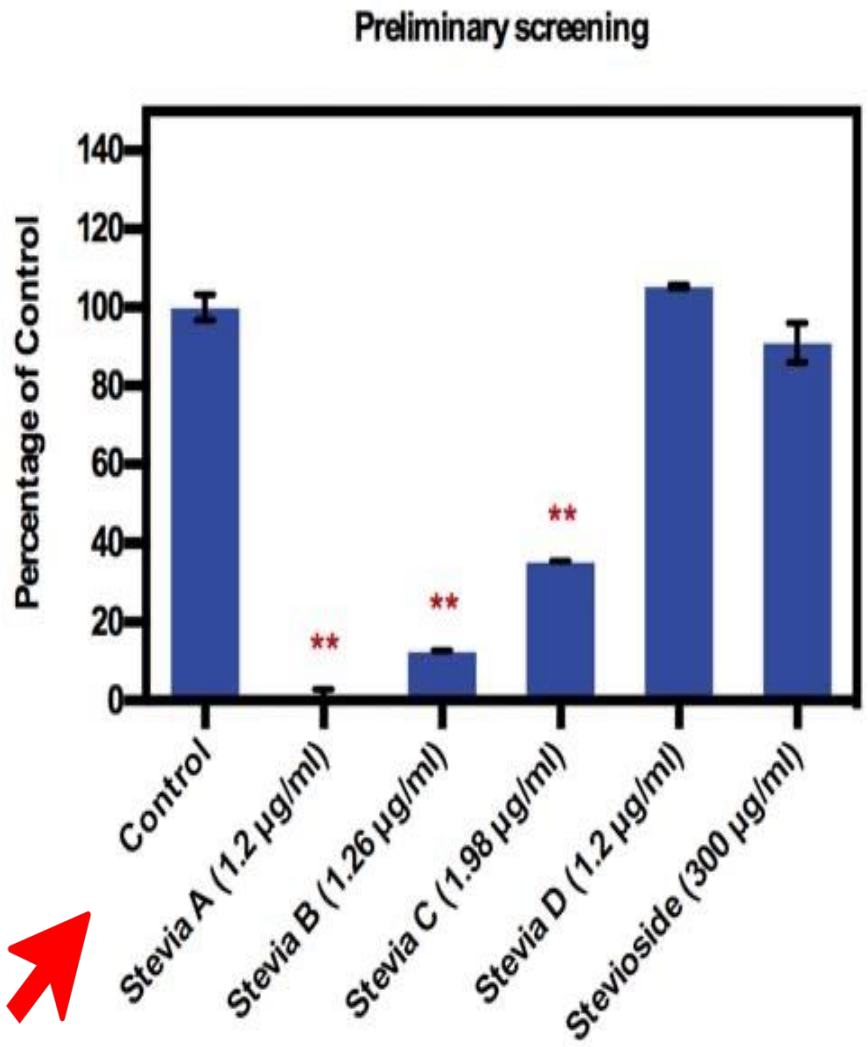
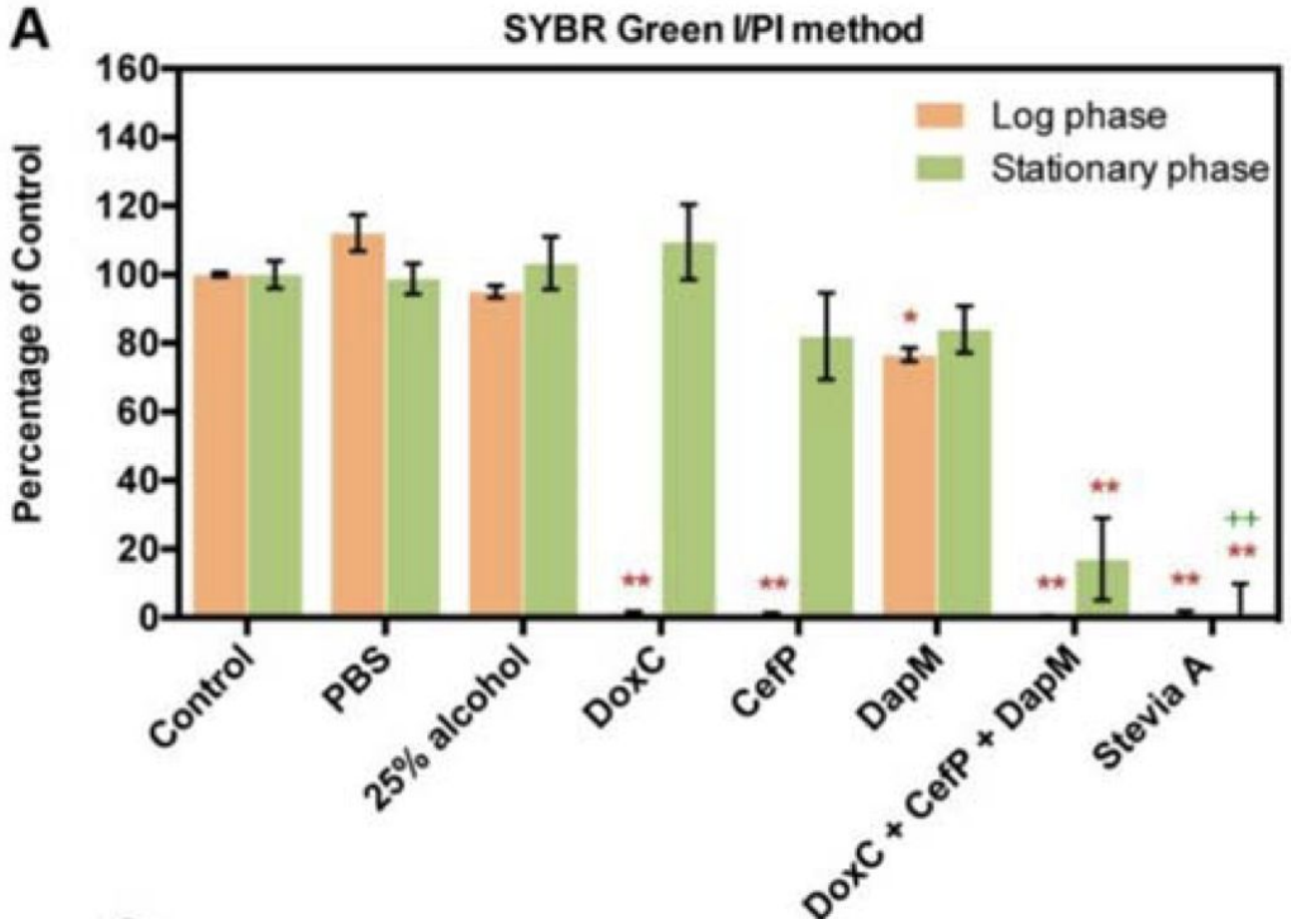
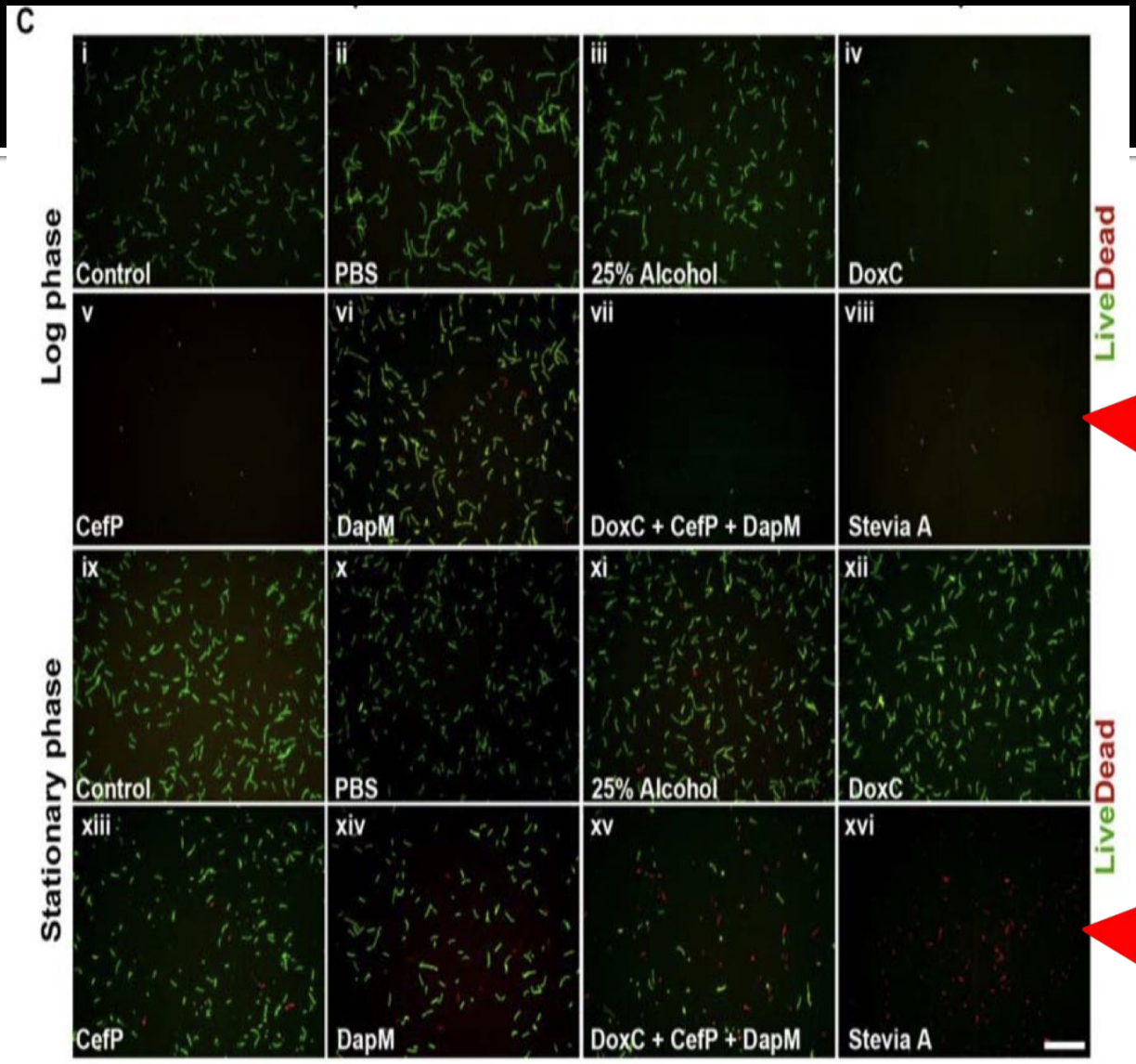


Fig. 1. Preliminary screening of four different extracts of Stevia and Stevioside on the stationary phase of B. burgdorferi after a three-day treatment using the SYBR Green/PI assay. n = 3 ± SD, * $p \leq 0.05$,** $p \leq 0.01$ compared to the control (Theophilus et al., 2015)



Stevia A significantly eliminated the log phase spirochetes and the stationary phase persisters compared to the control (100% effect for both)

Theophilus, P. A., et al. (2015). **Effectiveness of Stevia Rebaudiana Whole Leaf Extract Against the Various Morphological Forms of Borrelia Burgdorferi in Vitro**. *European journal of microbiology & immunology*, *5*(4), 268–280.



The log phase and the stationary phase borrelia treated with **Stevia A had only dead cells**

Stevia A Reduces Viable Organisms Within Biofilm

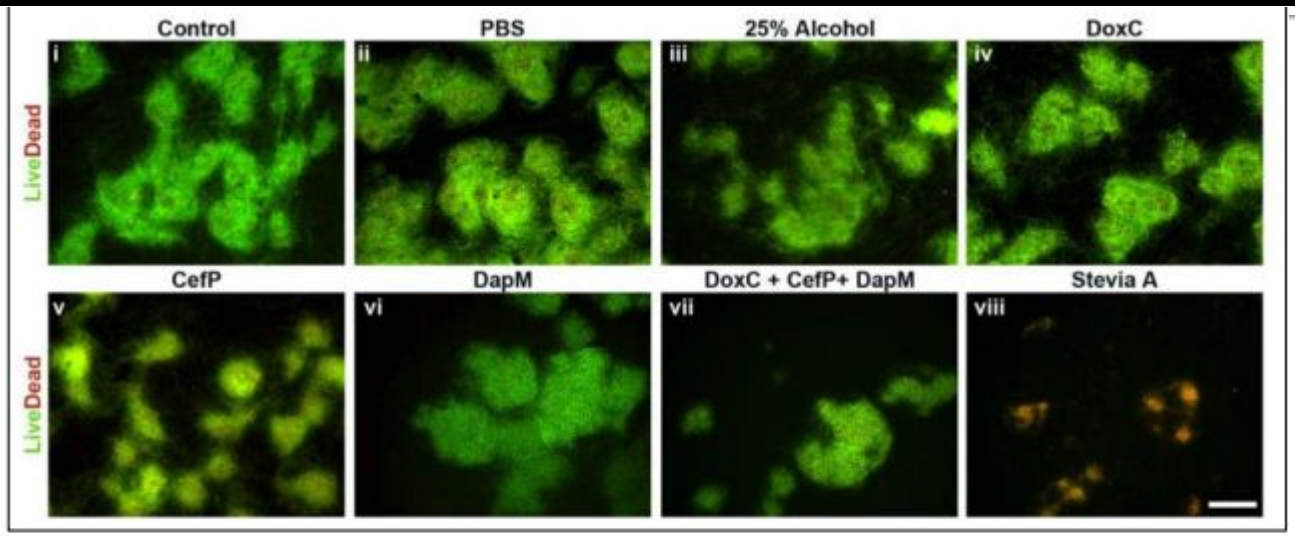


Fig. 5. Representative live/dead images of *Borrelia* biofilms treated with different antimicrobial agents followed by staining with SYBR Green I and PI dye mixture taken at 200× magnification. Doxycycline (DoxC) was used as a positive control. 1× sterile PBS and 25% alcohol were used as negative controls, respectively. All antibiotics individually as well as in combination were used at a concentration of 10 µg/ml. Stevia A was used at a concentration of 1.2 µg/ml. Scale bar −100 µm. *Abbreviations:* doxycycline – DoxC, cefoperazone – CefP, daptomycin – DapM

-The biofilms treated with individual antibiotics were predominantly green indicating living bacteria within them.

-The biofilms treated with the 3 antibiotic combination had a mixture of live and dead cells, with live cells predominating.

-**The biofilms treated with Stevia A stained predominantly red, depicting that the biofilm had mainly dead spirochetes /round bodies.**

Sapi E, Kaur N, Anyanwu S, Luecke DF, Datar A, Patel S, et al.: Evaluation of in-vitro antibiotic susceptibility of different morphological forms of Borrelia burgdorferi. Infect Drug Resist 4, 97–113 (2011)

Stevia for Metabolic Syndrome (in vivo)

- **Blood pressure** (Chan et al., 2000; Melis et al., 1997; Wong et al., 2006)
- **Satiety and healthier eating choices** (Ritu et al., 2016; Jeppesen et al., 2008)
  - More protein, less carbohydrate, fewer calories (human)
  - ↓ Weight (mouse)
- **Normalized Lipids** (Jeppesen et al., 2008; Ahmad et al., 2018; Adisakwattana et al., 2012)
  - ↓ Triglycerides
  - ↑ HDL
- **Blood sugar**
  - **Humans**: (Ritu et al., 2016; Pane et al., 2018; Gregersen et al., 2004)
  - **Animals**: (Toskulkao et al., 1995 [hamster]; Philippaert et al., 2017 [mice]; Jeppesen et al., 2006 [rats])
  - **↑ Insulin sensitivity**
  - **↓ Fasting and postprandial blood glucose**
  - **↓ Intestinal absorption of carbohydrate**

Stevia

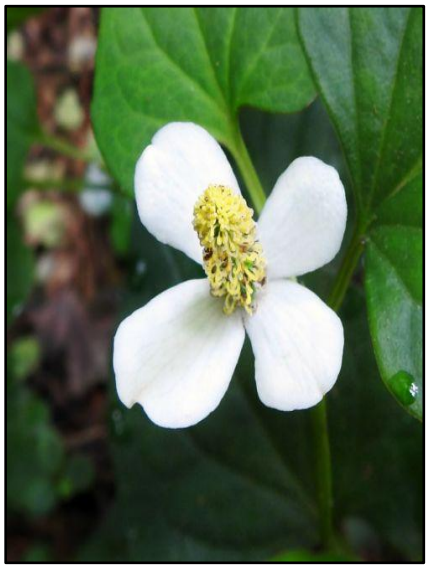
- **Inflammatory Response Support** (Boonkaewwan & Burodom, 2013)
  - Helps to normalize inflammatory cytokines such as TNF-alpha, IL-1-beta, IL-6 and NF-kappaB
- **Antioxidant Support** (Goyal et al., 2010)
  - Contains polyphenols and flavonoids that may help with oxidative stress
- **Safety and Cautions**
  - May increase lithium levels due to increased diuresis and decreased lithium excretion (theoretical) (Natural Medicines, 2021)
  - May have additive effects when taken concurrently with antidiabetic or antihypertensive medications (theoretical) (Natural Medicines, 2021)

NutraBRT = Cumanda + Houttuynia

- Cumanda, Houttuynia + minerals
- Effective against Bartonella & Mycoplasma, viruses, some parasites & fungi.

Houttuynia

- Yu Xing Cao / 鱼腥草
- *Houttuynia cordata* (leaves)

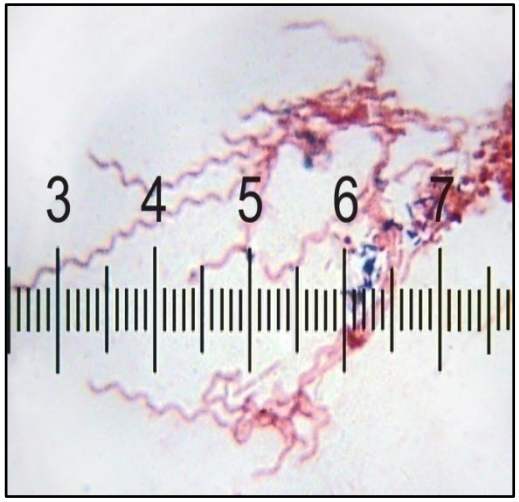


Houttuynia Microbial Support

(in vitro, in vivo)

- AntiBacterial
  - *S. aureus* *(Lu, 2006)*
  - *Sarcina ureae* *(Lu, 2006)*
  - *Propiniobacterium acnes* (*P. acnes*) (Chomnawang , 2007)
  - *Salmonella typhimurium* (Kim, 2008)

(Li et al., 2017; Sekita et al., 2016)



20100905_211652_Spirochetes.jpg: Bob Blaylockderivative work: F. Lamiot, CC BY-SA 3.0 <https://creativecommons.org/licenses/by-sa/3.0>, via

Antiviral Effects of Houttuynia

- Coronaviruses including SARSCov2
- HSV-1 and HSV-2
- Human immunodeficiency virus (HIV)
- Epstein-Barr virus
- Human papillomavirus (HPV)
- Influenza viruses
- Zika virus (ZIKV)
- Human noroviruses (HuNoVs) significantly suppressed the infectivity of MNV-1 to an undetectable level.
- Respiratory Syncytial Virus (RSV)
- Dengue virus
- Enterovirus 71
- Coxsackievirus A16, causative agents of hand, foot, and mouth disease

- Laldinsangi C. The therapeutic potential of *Houttuynia cordata*: A current review. Heliyon. 2022 Aug 24;8(8):e10386. doi: 10.1016/j.heliyon.2022.e10386. PMID: 36061012; PMCID: PMC9433674.

Houttuynia

- Inhibitory effects on anaphylactic reaction and mast cell activation.(Chou et al, 2009)
- **Immune and Inflammation Support** (Shingnaisui et al., 2018; Lee et al., 2013; Chun et al., 2014)
  - Helps to normalize inflammatory cytokines
    - Decreases Free radicals (Kim et al., 2008)
    - Balances CD_4 helper T cells and CD8 cells (Lau et al., 2008)
    - Healthy Th1/Th2 ratio (Lee et al., 2008)
    - IgE modulation (Han et al., 2009)
  - Balances Th17/Treg (regulatory T) cells
- **Gastrointestinal Support** (Zhu et al., 2018; Shi et al., 2020; Chen et al., 2019; Jiang et al., 2004)
  - Maintains healthy intestinal muscosa
  - Supports intestinal lymph tissue (GALT)
  - Supports a **healthy microbiome**
  - Supports normal transit time
- **No known contraindications, toxicity, or interactions**

Nat Immunol. 2024 Jan 11. doi: 10.1038/s41590-023-01724-6. Online ahead of print.

Long COVID manifests with T cell dysregulation, inflammation and an uncoordinated adaptive immune response to SARS-CoV-2

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Affiliations + expand

PMID: 38212464 DOI: 10.1038/s41590-023-01724-6

Abstract

Long COVID (LC) occurs after at least 10% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, yet its etiology remains poorly understood. We used 'omic" assays and serology to deeply characterize the global and SARS-CoV-2-specific immunity in the blood of individuals with clear LC and non-LC clinical trajectories, 8 months postinfection. We found that LC individuals exhibited systemic inflammation and immune dysregulation. This was evidenced by global differences in T cell subset distribution implying ongoing immune responses, as well as by sex-specific perturbations in cytolytic subsets. LC individuals displayed increased frequencies of $CD4^+$ T cells poised to migrate to inflamed tissues and exhausted SARS-CoV-2-specific $CD8^+$ T cells, higher levels of SARS-CoV-2 antibodies and a mis-coordination between their SARS-CoV-2-specific T and B cell responses. Our analysis suggested an improper crosstalk between the cellular and humoral adaptive immunity in LC, which can lead to immune dysregulation, inflammation and clinical symptoms associated with this debilitating condition.

Long-COVID (LC) individuals exhibited perturbations in both total and SARS-CoV-2-specific CD4+ and CD8+ T cells and changes in gene expression among CD4+ T cells, CD8+ T cells, monocytes and B cells.
We found higher proportions of CD4+ TCM cells, TFH, cells and Treg cells in LC compared to recovered (R) individuals. SARS-CoV-2-specific CD8+ T cells, but not total CD8+ T cells, more frequently expressed exhaustion markers, consistent with ongoing stimulation by viral antigens.
Further supporting a potential persistent reservoir was our observation of higher SARS-CoV-2 antibody levels in LC individuals, consistent with reports of higher spike-specific IgG in LC compared to R individuals."
The authors do not mention the vaccine status of the study subjects.

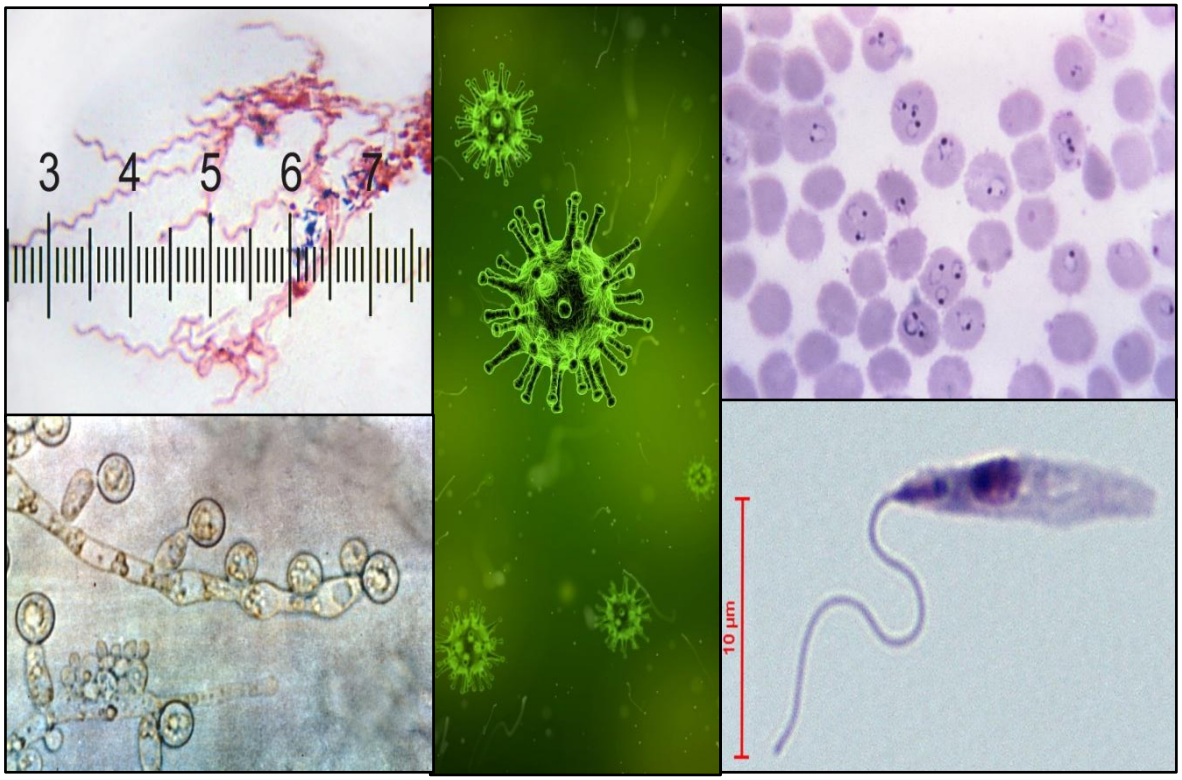
Yin K, Peluso MJ, Luo X, Thomas R, Shin MG, Neidleman J, Andrew A, Young KC, Ma T, Hoh R, Anglin K, Huang B, Argueta U, Lopez M, Valdivieso D, Asare K, Deveau TM, Munter SE, Ibrahim R, Ständker L, Lu S, Goldberg SA, Lee SA, Lynch KL, Kelly JD, Martin JN, Münch J, Deeks SG, Henrich TJ, Roan NR. Long COVID manifests with T cell dysregulation, inflammation and an uncoordinated adaptive immune response to SARS-CoV-2. Nat Immunol. 2024 Jan 11. doi: 10.1038/s41590-023-01724-6. Epub ahead of print. PMID: 38212464.

Cumanda

Campsiandra angustifolia
(bark)

Cumanda

- **Bacterial**
  (Theophilus & Sapi, 2013)
- **Parasitic**
  (Roumy et al, 2007; Kvist et al., 2006)
- **Fungal**
- **Viral**



20100905_211652_Spirochetes.jpg: Bob Blaylockderivative work: F. Lamiot, CC BY-SA 3.0

Candida albicans: GrahamColm, CC BY-SA 3.0 <https://creativecommons.org/licenses/by-sa/3.0>, via Wikimedia Commons

Stefan Walkowski, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons

Image Credit (malaria): This thin film Giemsa stained micrograph depicts afalciparum number of ring-form Plasmodium trophozoites. Creator: CDC/ Steven Glenn, Laboratory & Consultation Division.

Cumanda

- 82.2% as effective as ibuprofen/Advil for inflammation
- 112% as effective as celecoxib/Celebrex for inflammation
- (Allende, 2005)

Baikal Skullcap

- **Latin name**: *Scutellaria baicalensis* (root)
- **Common name**: Baikal skullcap
- **History**:
  - Known as "huang qin" in TCM
  - First known medicinal use dating back to the 2nd century C.E.
- **Not to be confused with**: American skullcap (*Scutellaria laterifolia*), which has different properties and is not interchangeable.

Use in Traditional Asian Medicine

- Used in traditional Chinese medicine for the following (Zhao et al., 2016):
  - Diarrhea
  - Dysentery
  - Hemorrhage
  - Hypertension
  - Inflammation
  - Insomnia
  - Respiratory infections

- Baicalin is a **Flavonoid.**
- Pharmacological properties of flavonoids include:
  - antioxidant
  - anti-inflammatory
  - anticancer
  - antimicrobial
  - immune modulation
  - (Panche,2016)

Baikal Skullcap

- **Antibacterial**
  - ***Staphylococcus aureus; E. coli*** (by inhibition of LPS and decreasing inflammatory cytokines) (Wang et al., 2018)
  - ***H. pylori*** (Dmitrieva et al., 2023)
  - ***M*any oral bacteria** (Chmiel et al., 2023)
  - **Lyme: active spirochetes, stationary forms, round bodies, and biofilms** (Feng et al., 2020; Goc et al., 2016)

Baikal Skullcap (*Babesia duncani*)

- In vitro, **baicalein was superior to standard therapy** (quinine and clindamycin) for *B. duncani* (Zhang et al., 2021).

TABLE 2 | The differing IC_{50} values indicated that *Cryptolepis sanguinolenta*, *Artemisia annua*, and *Scutellaria baicalensis* showed different inhibitory effects in 30%, 60%, and 90% ethanol extracts.

Natural product extracts	IC_{50} values
Cryptolepis sanguinolenta (30% EE)	0.039% (v/v)
Cryptolepis sanguinolenta (60% EE)	0.0041%
Cryptolepis sanguinolenta (90% EE)	0.0046%
Artemisia annua (30% EE)	0.0091%
Artemisia annua (60% EE)	0.0097%
Artemisia annua (90% EE)	0.030%
Scutellaria baicalensis (30% EE)	0.034%
Scutellaria baicalensis (60% EE)	0.038%
Scutellaria baicalensis (90% EE)	0.0097%
Cryptolepine	3.4 μM
Artemisinin	14 μM
Baicalein	12 μM
Quinine	10 μM
Clindamycin	37 μM

Growth was evaluated by SYBR Green stain at day three after B. duncani exposure to natural product extracts. Each natural product concentration was made in triplicate. IC_{50} values were calculated in GraphPad Prism (version 7.0). EE, ethanol extract.

IC_{50}

Half maximal inhibitory concentration
Indicates how much of a substance is needed to inhibit a biological component by 50%.

Baikal Skullcap

- **Antiviral** (Huang et al., 2023; Konoshima et al., 1992; Wang et al., 2018)
  - **Chikungunya Virus**
  - **Cytomegalovirus (CMV)**
  - **Dengue (DENV)**
  - **Hepatitis B Virus (HBV)**
  - **Human Immunodeficiency Virus (HIV)**
  - **Herpes Simplex Virus 1 (HSV-1)**
  - **Human T-Lymphotropic Virus (HTLV-1)**
  - **Influenza A**
  - **Rotavirus**
  - **Tick-borne Encephalitis Virus (TBEV)**
  - **Zika Virus (ZIKV)**
  - **Epstein-Barre Virus (EBV)**
    - **" flavones obtained from the root of Scutellaria baicalensis … showed remarkable inhibitory effects on the EBV-EA activation".**
    - Konoshima T, Kokumai M, Kozuka M, Iinuma M, Mizuno M, Tanaka T, Tokuda H, Nishino H, Iwashima A. Studies on inhibitors of skin tumor promotion. XI. Inhibitory effects of flavonoids from Scutellaria baicalensis on Epstein-Barr virus activation and their anti-tumor-promoting activities. Chem Pharm Bull (Tokyo). 1992 Feb;40(2):531-3. doi: 10.1248/cpb.40.531. PMID: 1318792

Baikal Skullcap

- **Antiviral** (cont.)
  - **Enterovirus EV-A71** (Li et al., 2015).
  - **IC_{50} of 4.96 µg/mL.**
- **Antifungal**
  - ***Candida albicans*** (Wang et al., 2018)
  - ***Candida* spp., *Aspergillus fumigatus*, *Trichophyton rubrum*** (Chmiel et al., 2023)

"The IC50: an exactly defined measure of antibiotic sensitivity" J S Soothill[1], R Ward, A J Girling DOI: 10.1093/jac/29.2.137
IC50 measures potency. How much of the substance is required to inhibit the microbe by 50%. Lower is stronger.

Anti-Inflammatory Support

- **Baicalin inhibits**
  - **NF-KB** (Zhou et al., 2014).
    - Lyme uses NF-KB to break down the tissues it needs to feed itself (i.e. collagen).
  - **TNF-alpha** (Zhou et al., 2019)
    - TNF-alpha affects the HPA axis and causes neurotoxicity and CNS damage.
  - **IL-1-beta** (Zhou et al., 2014)
  - **IL-6** (Zhou et al., 2014)
    - IL-6 impairs the HPA axis leading to dysregulation and nerve death, which may contribute to neurodegenerative diseases like AD and MS.
  - **Matrix metalloprotein-9 (MMP-9)** (Zhou et al., 2014).
    - Borrelia also uses MMP's matrix proteinases (collagenases) to break down collagen to feed and reproduce.
  - **Cox-2**
  - **IL-17** (Liao et al., 2016)
- **Baicalin upregulates**
  - **Heat shock protein 70** (Chen et al., 2006)

Baikal Skullcap Neurological Support

- **Various studies** have shown baicalin to have a **potent neuroprotective effect** against neuronal injury, **in vitro and in vivo** (Sowndhararajan et al., 2018).
- Baicalin **may help protect against neurodegenerative diseases** through various mechanisms, including the inhibition of oxidative stress, excitotoxicity, apoptosis, and inflammation (Sowndhararajan et al., 2018).
- In vitro studies revealed that both baicalin and baicalein caused a dose-dependent **decrease in amyloid-beta toxicity** by three different assays (Heo et al., 2004).
- It **may also help stimulate neurogenesis and promote the expression of neuronal protective factors** (Sowndhararajan et al., 2018).
- **Antidepressant and Anti anxiety** properties (Zheljazkov et al, 2007)
- **Improves cognitive performance** (Zheljazkov et al, 2007)

Baikal Skullcap Neurological Support

- Baicalin has the ability to penetrate the blood-brain barrier (Sowndhararajan et al., 2018).
- Baicalin also reduced blood-brain barrier permeability (Zhou et al., 2014).

Baikal Skullcap Microbiome Support

- Baicalin helps **support beneficial intestinal microbiota**, specifically those that produce short-chain fatty acids (SCFAs) such as *Eubacterium* spp., *Subdoligranulum* spp., and *Butyricimonas* spp. (Ganguly et al., 2022).
- These healthy bacteria ferment resistant starch from the diet, creating SCFAs.
- SCFAs have many benefits (Nogal et al., 2021):
  - Gut barrier integrity
  - Glucose and lipid metabolism
  - Immune regulation
  - Decreased inflammation
  - Produce plasmalogens

Baikal Skullcap Safety Data

- Baikal skullcap has been used safely in doses up to 3.5 grams per day for up to 8 weeks (NatMed Pro, 2023)
- Non-toxic with documented clinical safety (Gol'Dberg et al, 1997, Smol'Ianinov et al. 1997)

- No hepatotoxicity in patients taking a whole herb formulation of *Scutellaria baicalensis* dosed at 1,335 mg per day for an average of 444 days (Puri et al., 2019).

- Human safety studies on baicalin have shown that doses between 200–800 mg per day are safe and well-tolerated with a favorable pharmacokinetic profile (Li et al., 2014; Pang et al., 2016).

  - Some constituents bind with GABA receptors; sedation is possible but not expected (Hui et al., 2002)

  - May increase the metabolism of CYP2E1-, CYP1A2-, and CYP2C19-dependent drugs (Zhou et al., 2021)

Root Cause Combo

Root Cause Combo

- **Glucomedix**
- **Nutra BRT**
- **Baikal Skullcap**
- **Burbur / Pinella**
- **Standard Protocol**
- Start with 1 drop, 2x daily of each herb (1, 2 and 3) at least 30 minutes before food, if possible.
  Add 1 dropperful of Burbur / Pinella (4) with each dose.
  Put all the herbs together in a small amount of water.
  Increase each day by 1 drop, working up slowly to target dose (based on age below).

- * Hold the current dose if patient is experiencing new or worsening symptoms (Herxheimer reaction). Try 4 dropperful of Burbur / Pinella added to water bottle and drink throughout the day, if needed. Do not increase dosage until symptoms subside.

  Once you reach target dose, continue this protocol 2-4 months after symptoms resolve.
  It is recommended to titrate off each herb one at a time to make sure symptoms do not recur.

  Adult Dosage (age 12+)
  target dose of 40 drops, 2x daily.

  Children's Dosage (ages 6-12)
  target dose of 20 drops, 2x daily.

- **Protocol for Children (ages 2-6)**
  target dose of 10 drops, 2x daily.

- **INDIVIDUALIZE CARE WITH YOUR PRACTITIONER AND ADJUST AS REQUIRED**
- **IF NO IMPROVEMENT, RECONSIDER YOUR DIAGNOSIS AND/OR TREATMENT APPROACH WITH YOUR MEDICAL PROVIDER**
- **IF NO IMPROVEMENT, TEST FOR MOLD, AND CONSIDER ADDING CRYPTOLEPIS AND/OR TAKUNA.**

Herbal Dosing Suggestions

- Patients start at ***1 drop of each "killing" herb*** twice daily, combined with 20 drops of burbur/pinella
- They increase by 1 drop twice daily until they have any ***new or worsening symptoms***
- They ***hold the dose until back to baseline*** and then resume increasing to the target dose of ***30-40 drops of each herb twice daily***. (B/P stays at 20 drops, with extra doses as needed)

Pediatric Dosing

- I use ½ the target dose for children as 6-12
- I use ¼ the target dose for children 2-6

- Stevia A may need to be dosed higher, but I am still assessing that.

Herxheimer Reaction

- **SLOW DOWN ANTIMICROBIALS**
  - Greater than 3-5 days is NOT a Herxheimer (Secondary Porphyria more likely)
- **Burbur/Pinella** (for lymphatic and glymphatic support/Herxheimer support and more!) 20 drops twice daily. Add extra doses for any new or worsening symptoms.
  - **Take one dropperful every 10 minutes for up to an hour for any new or worsening symptom during treatment. (6 droppersful in glass and drink over an hour)**
- May be used with additional support products such as curcumin, chlorella, glutathione, etc.
- **Chlorella**
- **Binders**

Resistant Cases

- Emotional Trauma
  - HeartMath, EMDR, Limbic Retraining Programs, etc.
  - Per Dr Yanuck: Detail focus >> L cortex persistent activation >> loss of R cortex activation >> more sympathetic nervous system activation >> more worry >> more detail orientation. This is a vicious cycle.
  - MUST CHANGE FOCUS AWAY FROM SYMPTOMS AND LEARNING ABOUT THE ILLNESS!
- Coinfections
  - Address coinfections more aggressively
- MOLD, MOLD, MOLD!
  - Check home, school/work, church
  - OAT/Mycotoxin/Sinus/MARCONS testing
  - C4a and other labs
  - Treatment is avoidance, and may include binders, sinus sprays/rinses, antifungals

More Aggressive Bartonella

- **Houttuynia Plus Cumanda (Nutra BRT)**
- **Or Houttunia plus Cryptolepis (especially if babesia also present)**
- **Next, Add NM Stevia or Oregano Oil**
- **ADULT DOSING:**
- **Houttuynia** 1 drop 2 times a day and increase daily by 1 drop daily until at 30 drops 2 times a day.
- **Cumanda** 1 drop 2 times a day and increase daily by 1 drop daily until at 30 drops 2 times a day.
- **Cryptolepis** ¼ tsp 2 or 3 times a day and after 1 week, if tolerating it, increase to ½ tsp 2 or 3 times a day. May take up to 1 tsp three times daily, if required.
- **Stevia** 2 droppers twice daily for 2 months (2-2-2)
- **Oregano Oil** 1 pill 2 times a day (each capsule should include 75 mg of oregano).
- **May add Japanese Knotweed** 30 drops 2 times a day. (Prevents bartonella from moving deeper into the body)
- Bartonella Biofilm-Fibrin Nests: **Lumbrokinase (Bolouke)** 1 pill 2 times a day on empty stomach. May consider increasing the lumbrokinase to 2 pills 2 times a day after 1 month.

More Aggressive Mycoplasma

- Dr Cowden's Approach
- Samento and Cumanda
- Banderol and Stevia
- Rotate q2 weeks
- BUT hold the last 3 doses before each rotation (1 ½ days off)

Babesia

- Babesia will double every 24 hours if no treatment, so don't pause treatment!
- May be highly resistant to anti-malarial medications, so doctors may use up to 4 agents together!

More Aggressive Babesia

- Choose 2; treat for minimum of 4 months:
  - Baikal skullcap
  - Cryptolepis
  - Artemesia Annua (check liver first and periodically)
- Take with serrapeptase or lumbrokinase to address "nests".
- May start with meds: Mepron 750 mg bid with azithro 250 mg bid for 7 days.
  - And then follow with herbal regimen for 4 months due to high relapse rate.
- Babesia consumes hemoglobin, so may need to detoxify the excess iron (IP-6)
- Can also add berberine, Japanese knotweed, ECGC, sida acuta (watch thyroid and BP), *Allimed* 1 tid, *Allimax® Nutraceuticals, or Artemesinin* 400 mg FOR AVERAGE WEIGHT ADULTS (adjust by weight) 3 times daily pulsed 3-5 days in a row every 2 weeks.

Dr Nancy O'hara's Strep Approach

- Start with antibiotic (AZITHROMYCIN often) and then after 1 month add herbs (one at a time and see which 2 are best).
- Once herbs are close to full dose, start to wean antibiotics
- Dr O'Hara's favorite herbs for Strep:
  - Usnea - start with 1-2 drops and build up
  - Taiga - my favorite but hard to get;1 pill up to 4 pills/day
  - Berberine (Goldenseal)
  - Oregano Oil - tastes terrible so 1-2 pills (DFH or Biotics)
  - Neem - NEEM PLUS by Arush

Mast Cell Activation Syndrome Treatment

- Quercetin
- Luteolin
- Perilla Seed
- Chinese Skullcap
- DAO
- Baking Soda in water
- D3/K2
- SPM's (Pro-Resolving Mediators)
- Medications: Cromolyn sodium, Antihistamines (Both H1 and H2), Hydroxyzine
- Low histamine diet. Remember to avoid bone broth and leftovers. Also avoid food additives such as carrageenan, sodium benzoate, potassium sorbate, guar gum, xanthan gum
- Probiotics that contain bifida degrade histamine.

Mast Cell Activation Syndrome Treatment

- Dr Yanuck: **"Reduce the mast cell activation loop through degradation of the mitochondrial DNA fragments** (mtDNA's) that mast cells release into the GI tract during mast cell degranulation. Since the mtDNA's turn around and promote mast cell degranulation, breaking this loop can be a substantial advantage." **Via Bromelain or proteolytic enzymes**

OCD Supplements

- In OCD, too much glutamate results in thoughts getting "stuck" so you perseverate over those memories and think about them over and over again.
  - Lithium orotate
    - NOT the DRUG! This is a mineral that blocks the NMDA receptor, which is activated by glutamate. Therefore, lithium orotate calms the excitotoxicity caused by glutamate.
  - NAC, N-acetylcysteine
    - Stanford University reseasrch by Dr. Hardin using 2400 to 3600 milligrams of NAC was very helpful for ASD and OCD.
    - NAC adds glycine to glutamate to form glutathione.
    - NAC is an antioxidant that also helps with liver detoxification.

Case Study D.G.

- DG presented as a 10 year old female with complaint of headaches for 2 years, which had worsened significantly in the 8 months prior to visit.
- Also had repetitive behaviors develop 2 years ago.
  - ie continuously pulling up socks, head tossing, tics, obsessive picking of scabs.
- Also with abdominal discomfort ,very restricted eating/ few foods, continuous rhythmic, dance-like body movement.
- Other complaints include severe fatigue (lays on couch a lot), constipation (hard pellets), and mom notices that she twitches.

Case Study D.G.

- PE normal. Doesn't speak to me, but nods and smiles.
- Suspect PANDAS/PANS
- Labs Ordered: CBC, CMP, TSH, CRP, Homocysteine, B12, Ferritin, iron, rbc Mag, vit d, zinc, mma, celiac, histamine, anti-dnase b, anti-streptolysin Ab, MDL panel.
- Started on magnesium, samento, and IgG powder.
- Discovered a few gluten free foods that she could eat. (Fruit, corn chips, peanut butter, gluten free chicken nuggets, fries)

Case Study D.G.

- 3 week follow up:
  - No change in symptoms
- Labs revealed a B12 of 292 (low normal), Homocysteine 9.9
- Lyme WB negative with 41 band IgG and IgM positive
- I added SL methyl B12 and cumanda with burbur/pinella

Case Study D.G.

- One Month Later
- Some improvement. More active. Began skateboarding. Talking more. Laughing again.
- People outside family noticed.
- Rhythmic body movements have subsided.
- No further headaches.
- Appetite has improved.
- PE, very shy, but talks to me now.
- ea EBV now positive.
- Added monolaurin. Added japanese knotweed, resveratrol, stopped cumanda and then reduced samento to once daily.

Case Study D.G.

- 4 months later
- Feels even better than last visit. Doing so well that she reduced all supplements to once daily.
- No further tics.
- Playing basketball.
- Appetite continues to improve.
- All other symptoms completely resolved.
- B12 increased to 471 and Homocysteine improved to 6.3

- Released to annual follow-ups 4 years ago, but never returned. Mother and sister still come and state she is doing great, never regressed!

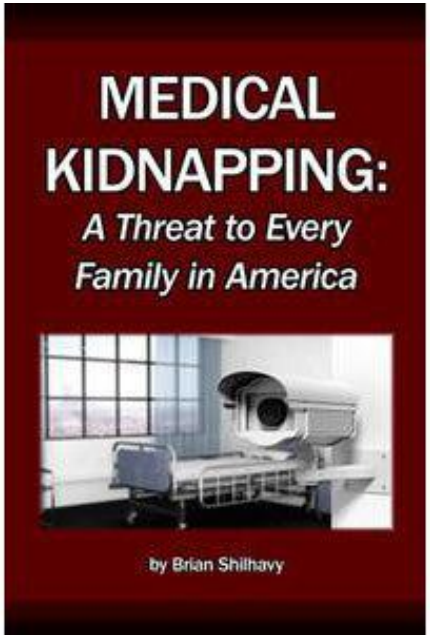
A Sister's Perspective

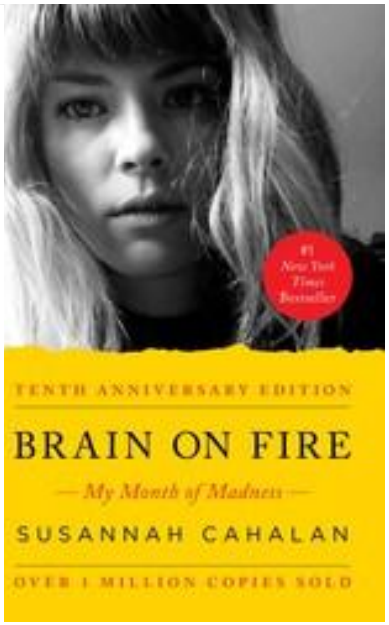
- My sister [RL] had PANS when she was 12 and I was 14. Which shattered our relationship as sisters.
- The PANS had effected her brain and mannerisms and made her think that I was sick.
- She wouldn't touch me, hug me, or touch anything I touched.
- She had her own set of dishes because she didn't want to use the ones I touched, she also had her own snack drawer so our food wouldn't be in the same area.
- If I coughed or yawned she would tick and cough three times then make some humming and rub her lips.
- This was so hard since we were once so close and now at 14 all I knew was a sister who treated me like a germ.
- There were moments where I didn't think we would ever have a good relationship again, I thought this was the way it was going to be for the rest of our lives.

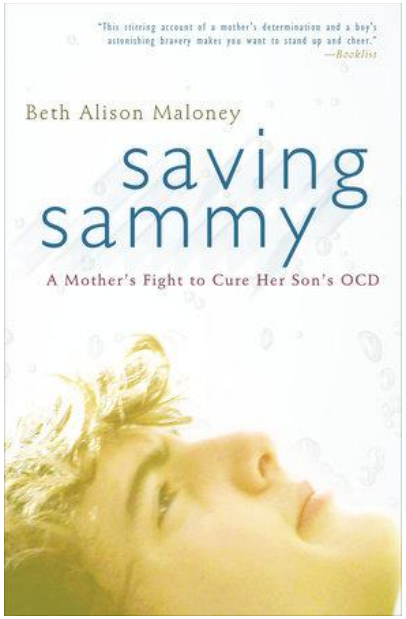
A Sister's Perspective

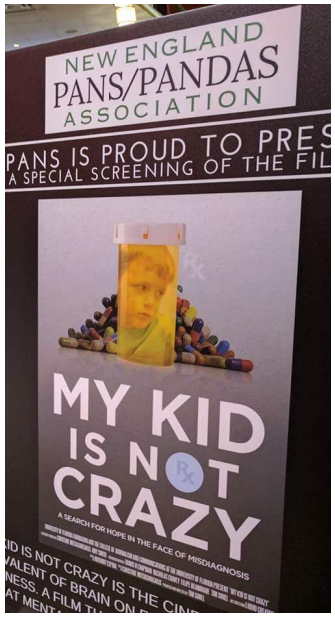
- Luckily through prayer and proper medical treatment it took two and a half years for her to heal.
- Now at 19 and 17 she steals my clothes, eats my food, borrows my things, and is honestly one of my best friends!
- If I would have known that in two and a half years we would be where we are now, I would have been so much more hopeful…
- It won't be this way forever.

Resources


MEDICAL KIDNAPPING:
A Threat to Every Family in America
by Brian Shilhavy


TENTH ANNIVERSARY EDITION
BRAIN ON FIRE
My Month of Madness
SUSANNAH CAHALAN
OVER 1 MILLION COPIES SOLD


Beth Alison Maloney
saving sammy
A Mother's Fight to Cure Her Son's OCD


NEW ENGLAND
PANS/PANDAS
ASSOCIATION
MY KID
IS NOT
CRAZY

Questions?

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