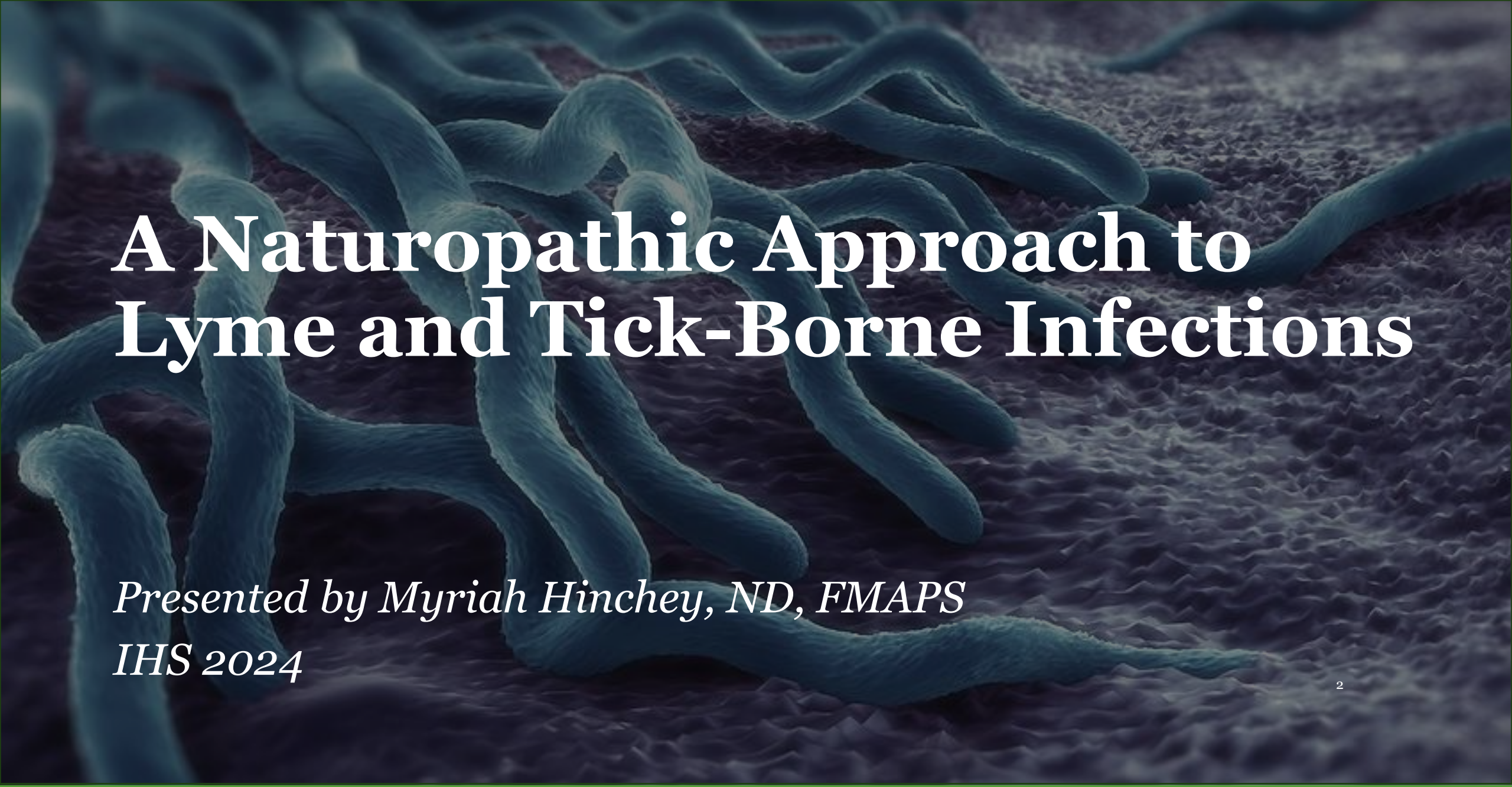
Naturopathic Treatment of Tick-Borne Disease: A Deep Dive into the Pathophysiology of Lyme Disease and Babesia and the MOAs of Herbal Intervention

Myriah Hinchey, ND, FMAPS



A Naturopathic Approach to Lyme and Tick-Borne Infections

Presented by Myriah Hinchey, ND, FMAPS

IHS 2024

Disclosures

I disclose the following relevant financial or non-financial relationships:

- TAO: Center for Vitality, Longevity, & Optimal Health (Founder, Owner, Medical Director)
- LymeCore Botanicals (Co-founder, Owner)
- LymeBytes (Founder, Owner)

Any reference to off-label or non-FDA approved usage in this presentation will be noted and disclosed.

Lecture Objectives

Discuss	Review	Demonstrate	Illustrate	Present
Discuss common myths and symptom recognition of Lyme disease	Review the pathophysiology of Borrelia spp and Babesia spp	Demonstrate the MOA of commonly used herbs and supplements • How they block the movement of infection, normalize the immune system, and are used to heal the body	Illustrate how infections as well as lifestyle plays a role in making the patient hospitable to infection • How to alter the body's biochemistry to make the body inhospitable to infection	Present a comprehensive naturopathic protocol for healing from Lyme and Babesia

Common Myths

Only deer ticks transmit Lyme disease (Pritt et al., 2016).

Reality: While the black-legged tick (or deer tick) is the primary vector of Lyme disease in the U.S., other ticks can also carry and transmit the disease.

A bull's-eye rash is needed to diagnose Lyme disease (Wormser et al., 2006).

Reality: Not everyone with Lyme disease develops the characteristic erythema migrans (bull's-eye) rash. Many people may have atypical rashes, and some may have no visible rash at all.

If the tick is removed within 24 hours, you can't get Lyme (Steere et al., 2004).

Reality: While the risk of transmission is lower if the tick is removed quickly, it is not zero. It's always essential to monitor for symptoms and seek medical advice if concerned.

All Lyme cases are acute and easy to diagnose(Marques, 2008).

Reality: Lyme can manifest as chronic symptoms in some individuals, and diagnostic tests are not always conclusive.

Standard Lyme tests are accurate (Branda & Strle, 2018).

Reality: Commonly used tests, such as the ELISA and Western blot, can yield false negatives, especially in the early stages of the disease.

Common Myths

A few weeks of antibiotics will cure Lyme disease (Bransfield, 2005).

Reality: While many individuals recover with a standard course of antibiotics, some may require prolonged treatment, especially if the disease has progressed or if there are co-infections.

Only people in the northeastern U.S. are at risk for Lyme disease (Steere et al., 2004).

Reality: Lyme disease has been reported in all 50 U.S. states and many other countries around the world.

You can't have Lyme if you don't remember a tick bite (Steere et al., 2004).

Reality: Many people diagnosed with Lyme disease do not recall a tick bite. Ticks can be tiny and their bites painless, so they can easily go unnoticed.

Lyme disease is only a joint disease (Marques, 2010).

Reality: Lyme disease can affect multiple systems in the body, including the neurological, cardiac, and musculoskeletal systems.

Common Myths

Lyme disease is the only illness transmitted by ticks (Steere et al., 2016).

Reality: Ticks can transmit a variety of diseases, including anaplasmosis, babesiosis, bartonellosis, ehrlichiosis, and many others.

If you're treated for Lyme disease and still have symptoms, you must have another condition (Marques, 2010).

Reality: Some people develop a set of ongoing symptoms called post-treatment Lyme disease syndrome (PTLDS) or "chronic Lyme" which can continue after initial treatment.

There is no such thing as chronic Lyme disease (Marques, 2010).

Reality: This is a controversial area. Some patients have persistent symptoms despite treatment, which can resemble chronic illness. The exact nature and cause of these symptoms, whether it's ongoing infection or an autoimmune-like response, are areas of ongoing research and debate.

For more info visit www.ILADS.com

Symptoms of Lyme Disease

Lyme Disease Association, Inc. (n.d.). Lyme Disease Symptoms. Retrieved from https://lymediseaseassociation.org/lyme-tbd/medical/lyme-disease-symptoms/

- Fatigue
- Headache
- Arthralgias, myalgias
- Cognitive deficits
- Depression/ Anxiety
- Sleep disruption
- Palpitations, rapid pulse
- Change in bowel function
- Pelvic pain
- Chest pain/ rib pain
- Twitching
- Hormone imbalance
- Irritable bladder
- Sweats
- Chills
- Short of breath
- Cough
- Dizziness
- Hair loss
- Thyroid issues
- Chronic sore throat/ swollen glands
- Intermittent blurry/ double vision
- Intermittent hearing issues/ ringing/ buzzing
- Sensitivity to EVERYTHING!

- **Symptoms are chronic but intermittent** and often affect multiple organ systems at once
- **Key diagnostic feature: symptoms are**
  - Multisystem
  - Migratory
  - Cyclic
- **Hallmark:** immune impairment that worsens over time
- **Pattern recognition is KEY!**

According to the CDC

(Centers for Disease Control and Prevention, 2021).

Lyme is the fastest growing epidemic we have been faced with and should be diagnosed based on:

1. **Symptoms and physical findings**
2. **Possibility of exposure to infected ticks**
3. **Laboratory tests are helpful in diagnosing Lyme disease, with the CDC recommending a two-step testing process**

This does NOT mean Lyme disease should be diagnosed based on a positive or negative test (which is often the case)!

Image retrieved from: https://sarctrials.org/

Key Points to Remember

EM RASH (IF PRESENT) IS DIAGNOSTIC OF LYME DISEASE. NO NEED TO TEST! BUT SHOULD STILL TEST FOR CO-INFECTIONS! TREATMENT IS NOT ALWAYS THE SAME.

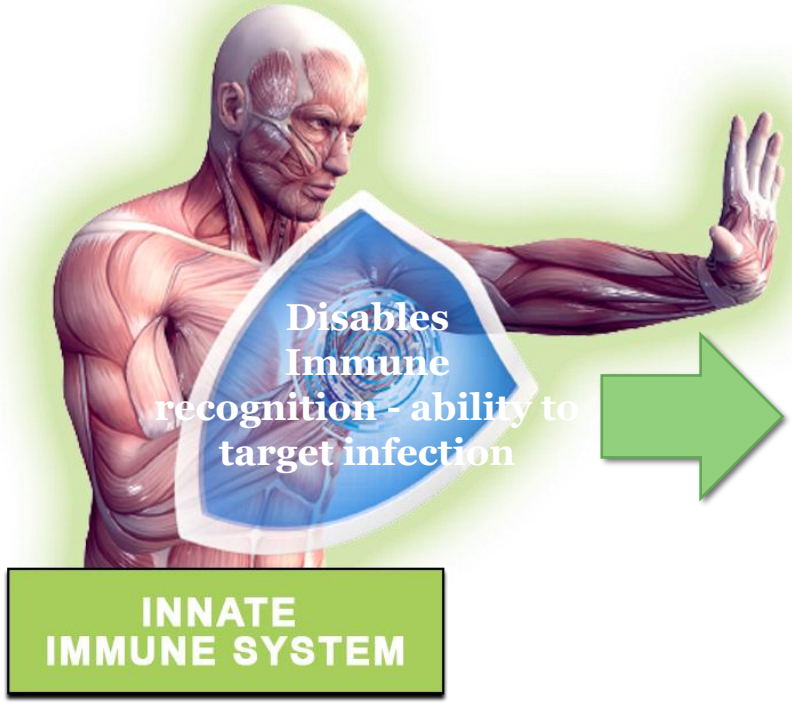
TESTING TOO EARLY CAN GIVE FALSE NEGATIVE. PEAK ANTIBODY PRODUCTION IS 3-6 WEEKS.

YOU CAN ONLY GET RESULTS FOR SPECIFIC SPECIES OF BORRELIA THE TEST LOOKS AT!

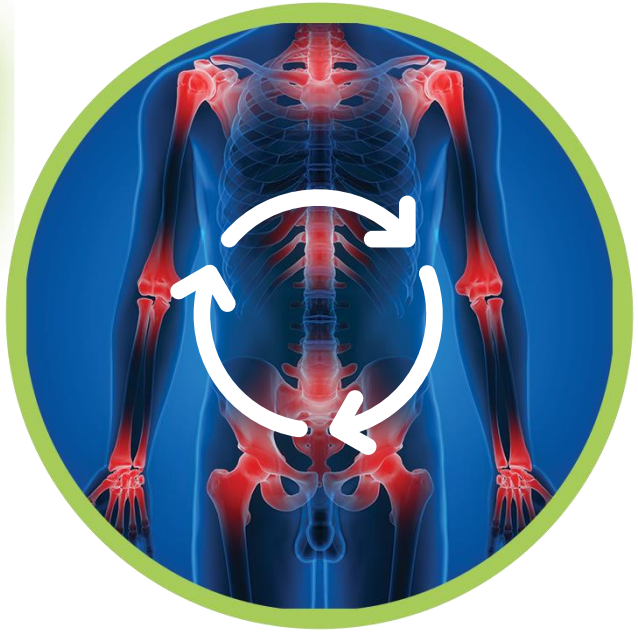
TESTING FOR LYME DOESN'T TEST FOR CO-INFECTIONS!

LOOK FOR OTHER LAB FINDINGS THAT MAY BE USEFUL IN YOUR DIAGNOSIS!

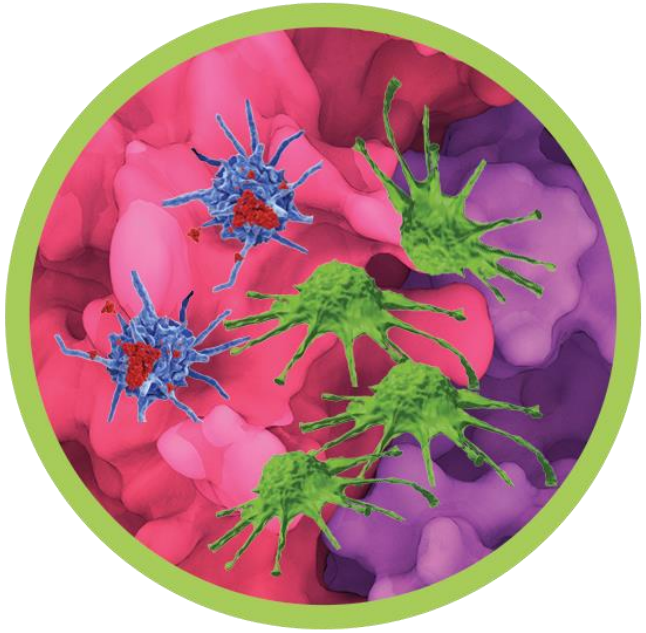
Immune Dysfunction is Often Behind Disappointing Clinical Outcomes



LYME/CO-INFECTIONS



ONGOING INFLAMMATORY RESPONSE



INCREASES INVASION PROLIFERATION IMMUNE SUPRESSION

Proprietary images created by Myriah Hinchey, 2023

Signs of Immune Dysfunction in Lyme

Signs that Lyme has weakened the immunity:

- ✓ **Low total WBC counts**
- ✓ **Depressed lymphocyte percent**
- ✓ **Low killer cell (NK cell) counts**
- ✓ **Decreased immunoglobulin levels (B cell impairment)**
- ✓ **Impaired T cell reactivity**
- ✓ **Persistent disease that responds poorly to meds that should work**

Signs that Lyme has activated the cytokines:

- ✓ **Everything!**
- ✓ **Malaise**
- ✓ **Fatigue**
- ✓ **Aches**
- ✓ **Cognitive impairment**
- ✓ **Neuropathy**
- ✓ **Arthritis**
- ✓ **Many more!**

How Lyme Disease Persists

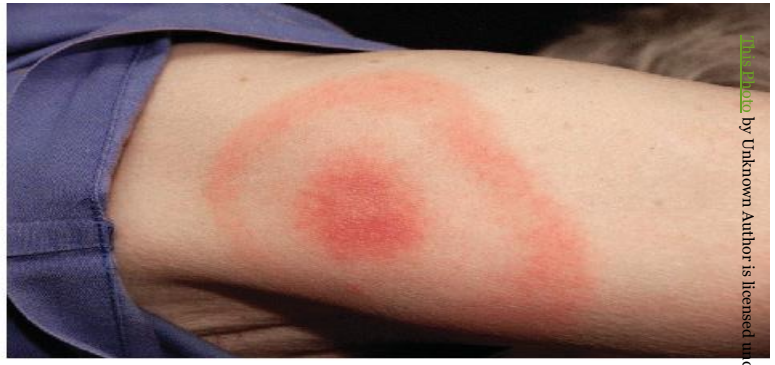
- Lyme and Co-infections hijack the immune system and get it to work for them instead of for the host in both the acute and chronic infection phases (Anderson et al., 2021)
- Lyme and co-infections release chemicals that work synergistically with the chemokines released from tick saliva at the time of initial infection (Cotté et al., 2014)
- Together they (tick saliva and infectious organisms) manipulate the biochemistry of the body using various enzymes to degrade the connective tissue matrix to feed themselves and alter the immune system ultimately making the body hospitable to the infection (Cotté et al., 2014)

Anderson C, Brissette CA. The Brilliance of Borrelia: Mechanisms of Host Immune Evasion by Lyme Disease-Causing Spirochetes. Pathogens. 2021 Mar 2;10(3):281. doi: 10.3390/pathogens10030281. PMID: 33801255; PMCID: PMC8001052.

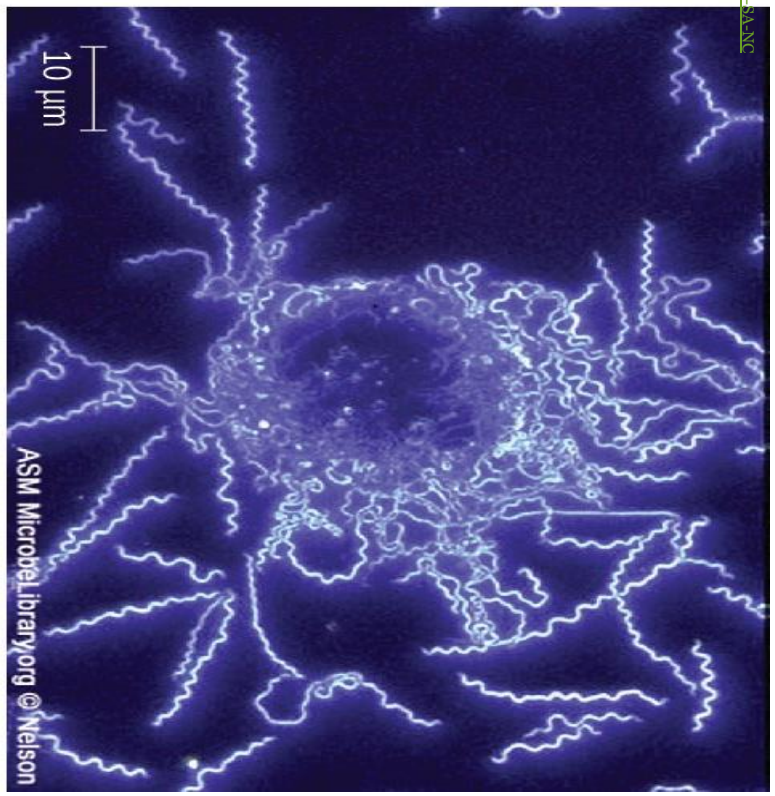
Cotté, V., Sabatier, L., Schnell, G., Carmi-Leroy, A., Rousselle, J. C., Arsène-Ploetze, F., Malandrin, L., Sertour, N., Namane, A., Ferquel, E., & Choumet, V. (2014). Differential expression of Ixodes ricinus salivary gland proteins in the presence of the Borrelia burgdorferi sensu lato complex. Journal of proteomics, 96, 29–43. https://doi.org/10.1016/j.jprot.2013.10.033

Many Treatments Fail When…

- Focus is on killing the organism instead of healing the patient
- Not addressing the ROOT causes that are
  1. making the patient hospitable to the infection
  2. keeping the patient from healing
  3. inhibiting elimination of the infection(s)
- Relying on antibiotics to eradicate the infection
- We need to FOCUS on:
  1. normalizing the immune system
  2. making the body inhospitable to the infection
  3. HEALING the body…while killing the infectious organisms



This Photo by Unknown Author is licensed under CC BY-SA-NC



No combination or amount of antibiotics will COMPLETELY eradicate the infection; it's the body's immune system that must eliminate it from the body or put it into remission.

(Bernard 2018)

https://www.fdli.org/2019/07/new-dietary-ingredients-ndi-and-innovation-in-dietary-supplements/

Excessive Antibiotics Can Cause Further Immune Dysfunction By:

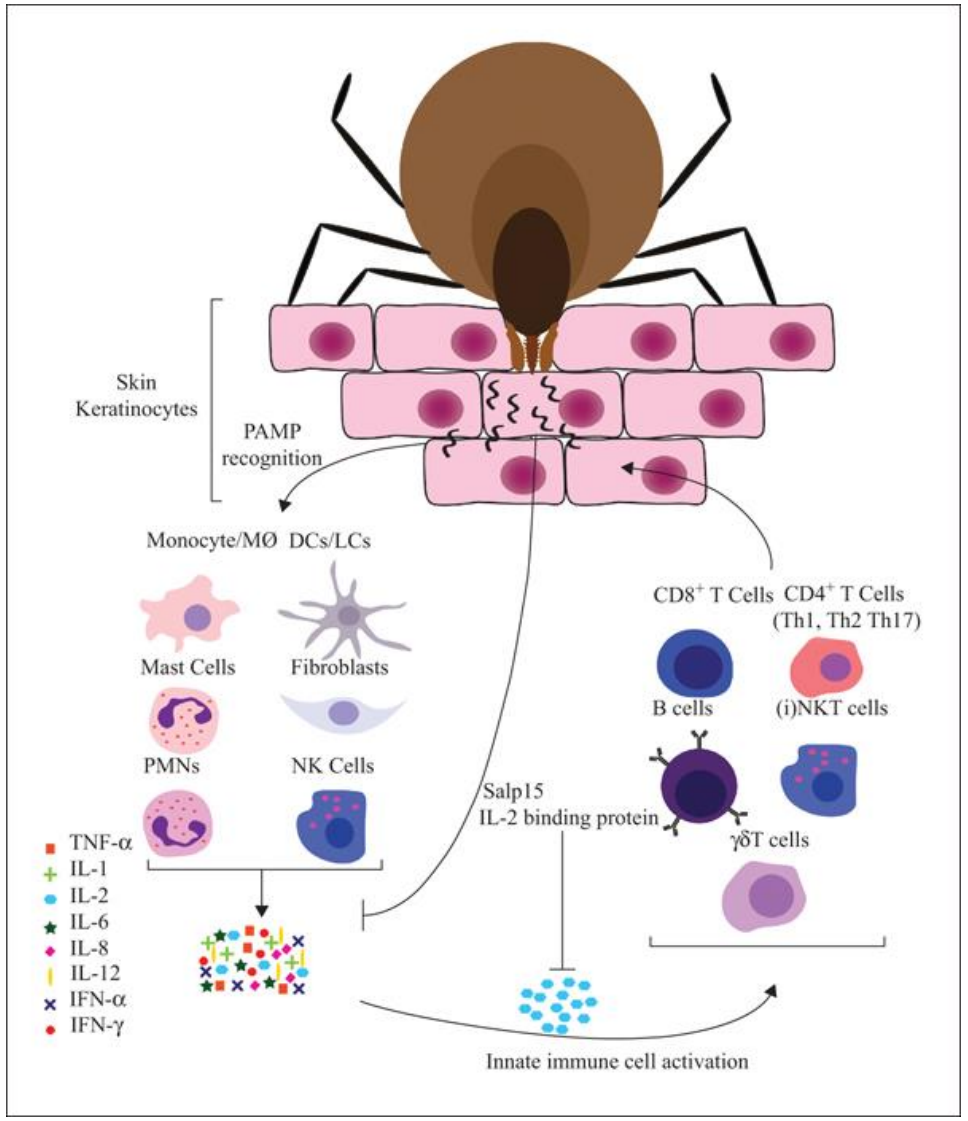
1. Disrupting the microbiome (Schwartz, 2020)
2. Increasing gut permeability (Aleman, 2023)
3. Increasing toxic load (Björnsson, 2017)
4. Impairing organs of detoxification and elimination (Björnsson, 2017)
5. Altering nutrient intake (Basolo, 2020)
6. Triggering formation of persister cells (Sharma, 2015)

How Do We Treat an Infection that Needs to be ***ELIMINATED***

While ***RESTORING*** Proper Immune Function…

Restoring Immune Function

Investigate the terrain of the individual and find out what pieces of the puzzle have been altered in that particular patient.



A Perfect Storm

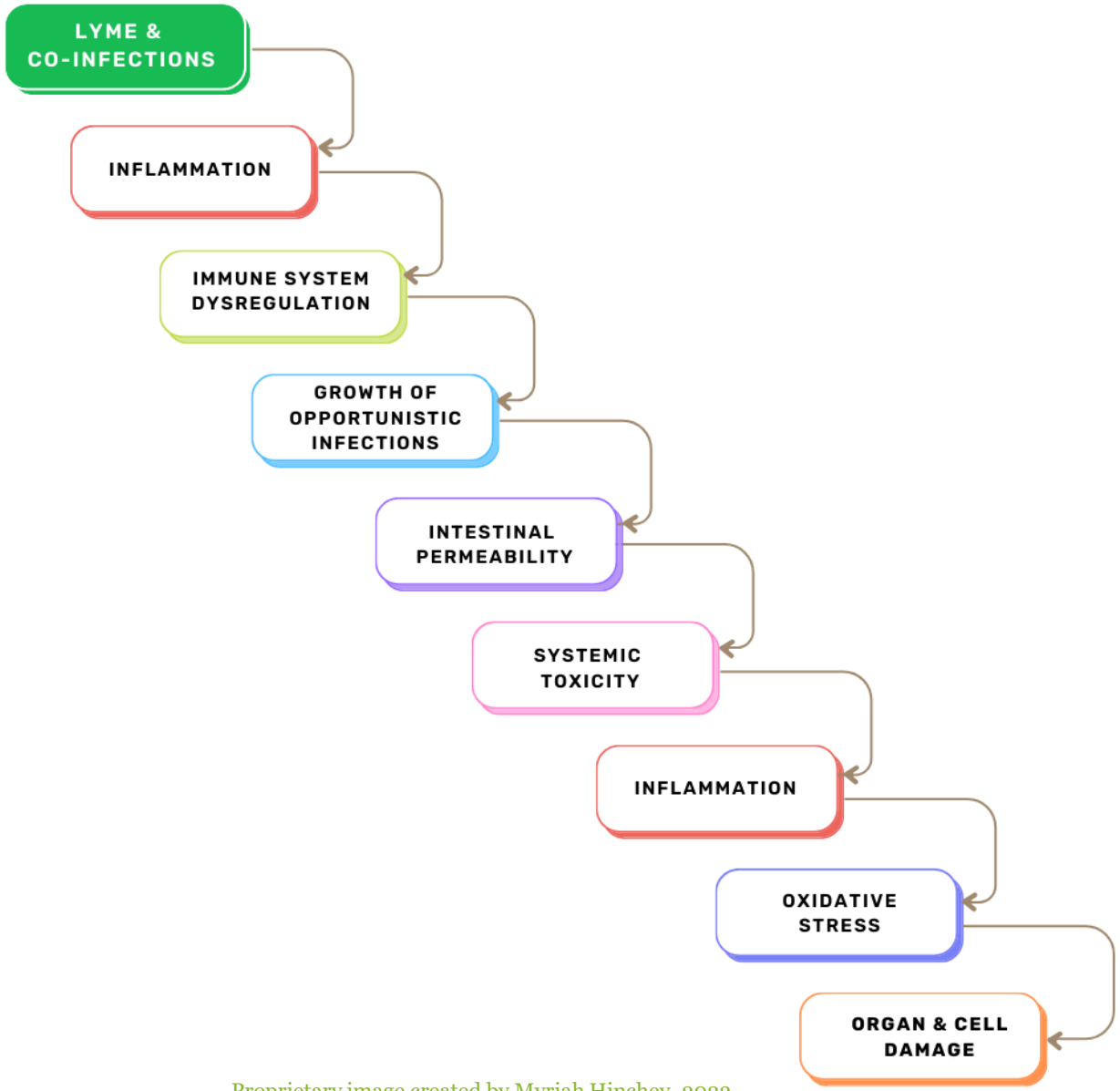
Image and Content:
Verhaegh, Dennis, et al. "The Role of Host Immune Cells and Borrelia Burgdorferi Antigens in the Etiology of Lyme Disease." *European Cytokine Network*, vol. 28, no. 2, June 2017, pp. 70–84., https://doi.org/10.1684/ecn.2017.0396.

- Immune dysregulation
- Inflammatory cytokine cascade
- Enzymes that breakdown collagen and ECM
- Elevated Galactin-3 levels
- Damage to endothelial cells
- Increased intestinal permeability
- Increased toxicity
- Formation of biofilms
- Eventual impairment of organs and organ systems

Cascade of Events

What we wish it were…

- A Linear Model of Events

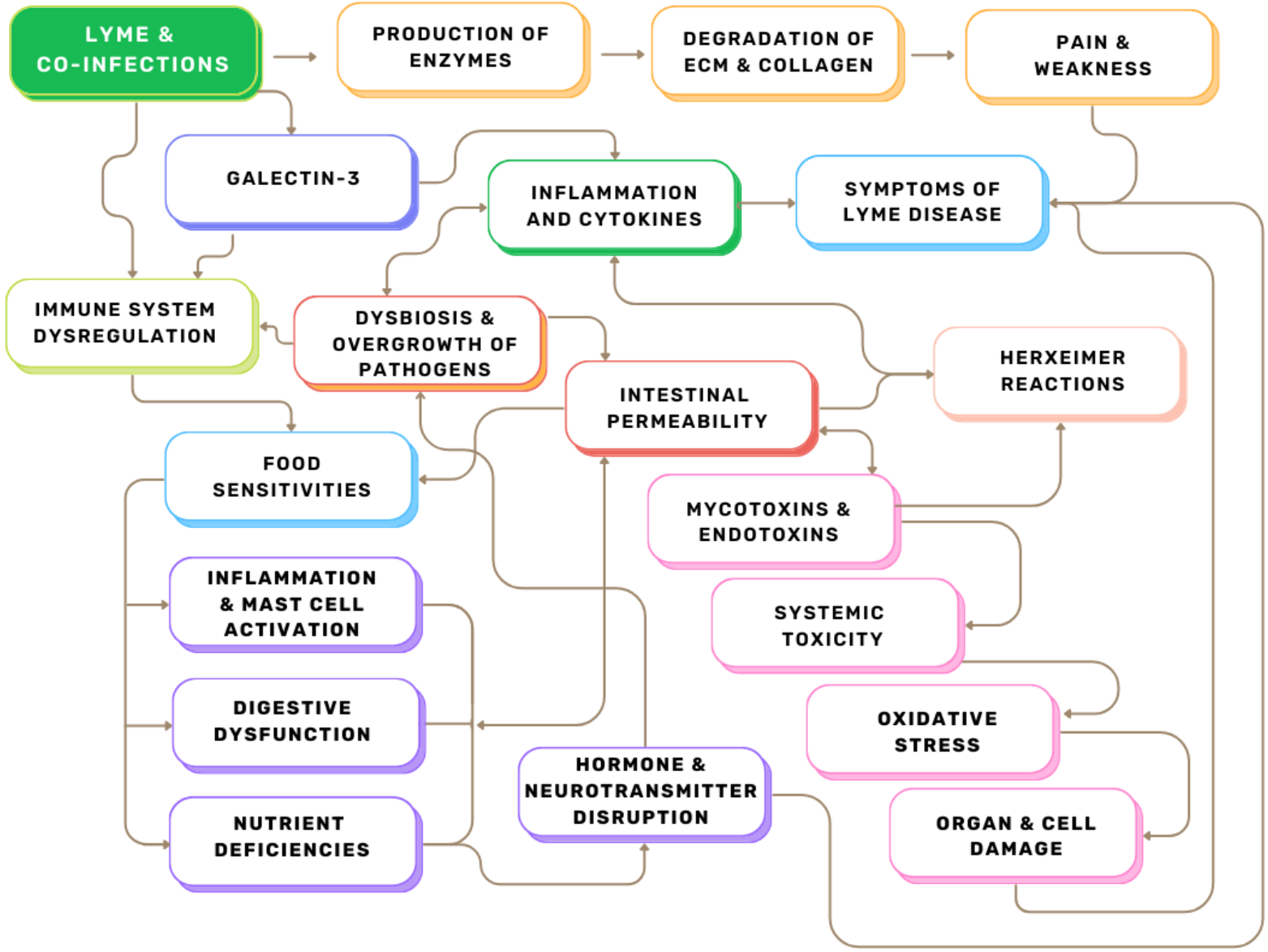


Proprietary image created by Myriah Hinchey, 2023

Cascade of Events

The Reality…

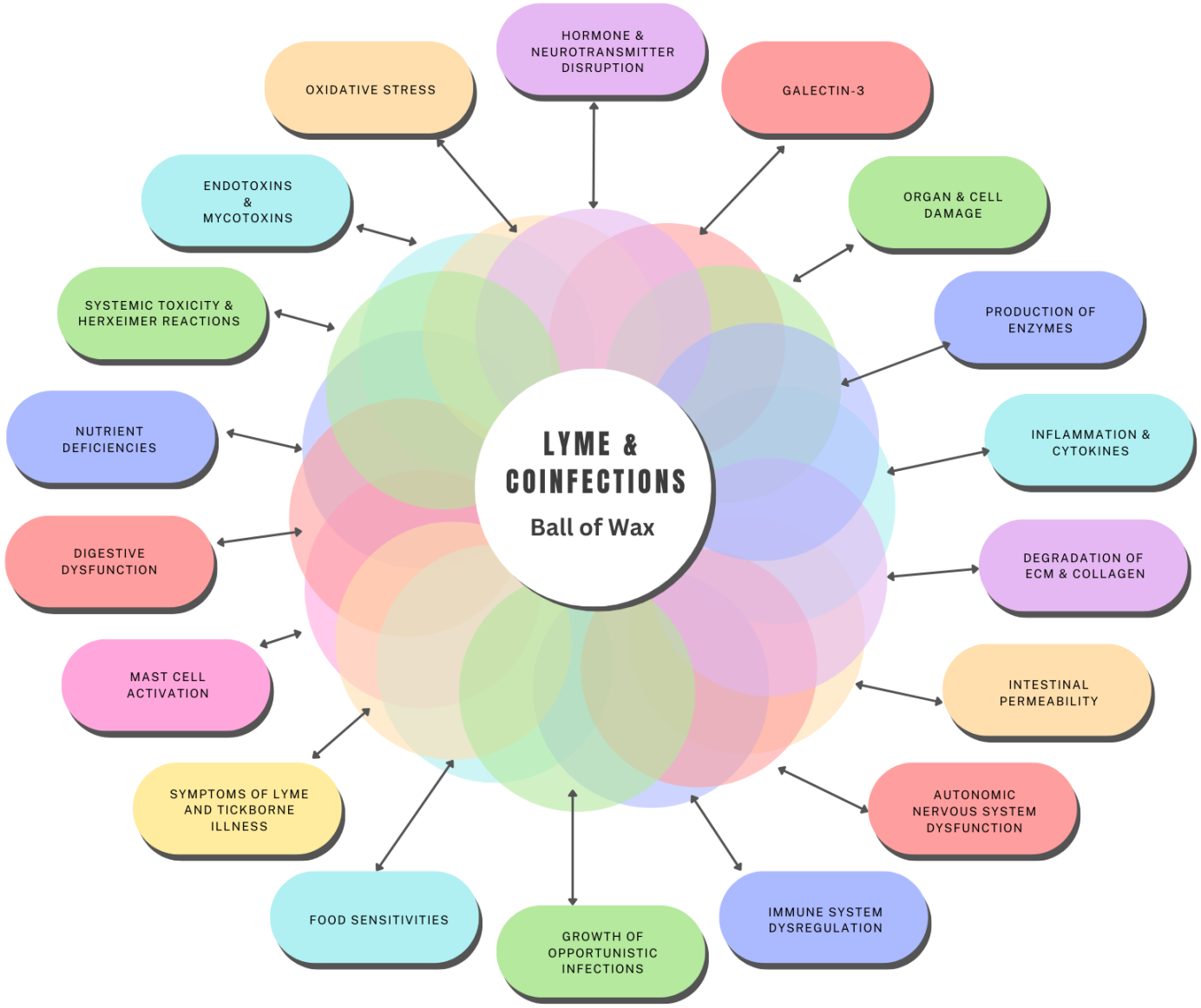
- A Hornet's Nest of Events
- Complex Pathophysiological Interactions



Proprietary image created by Myriah Hinchey, 2023

Making the Body Hospitable

TBD infections alter the terrain of the body to allow them not only to evade the immune system and survive but THRIVE!



These dysfunctions are intermingled and need to be dealt with simultaneously

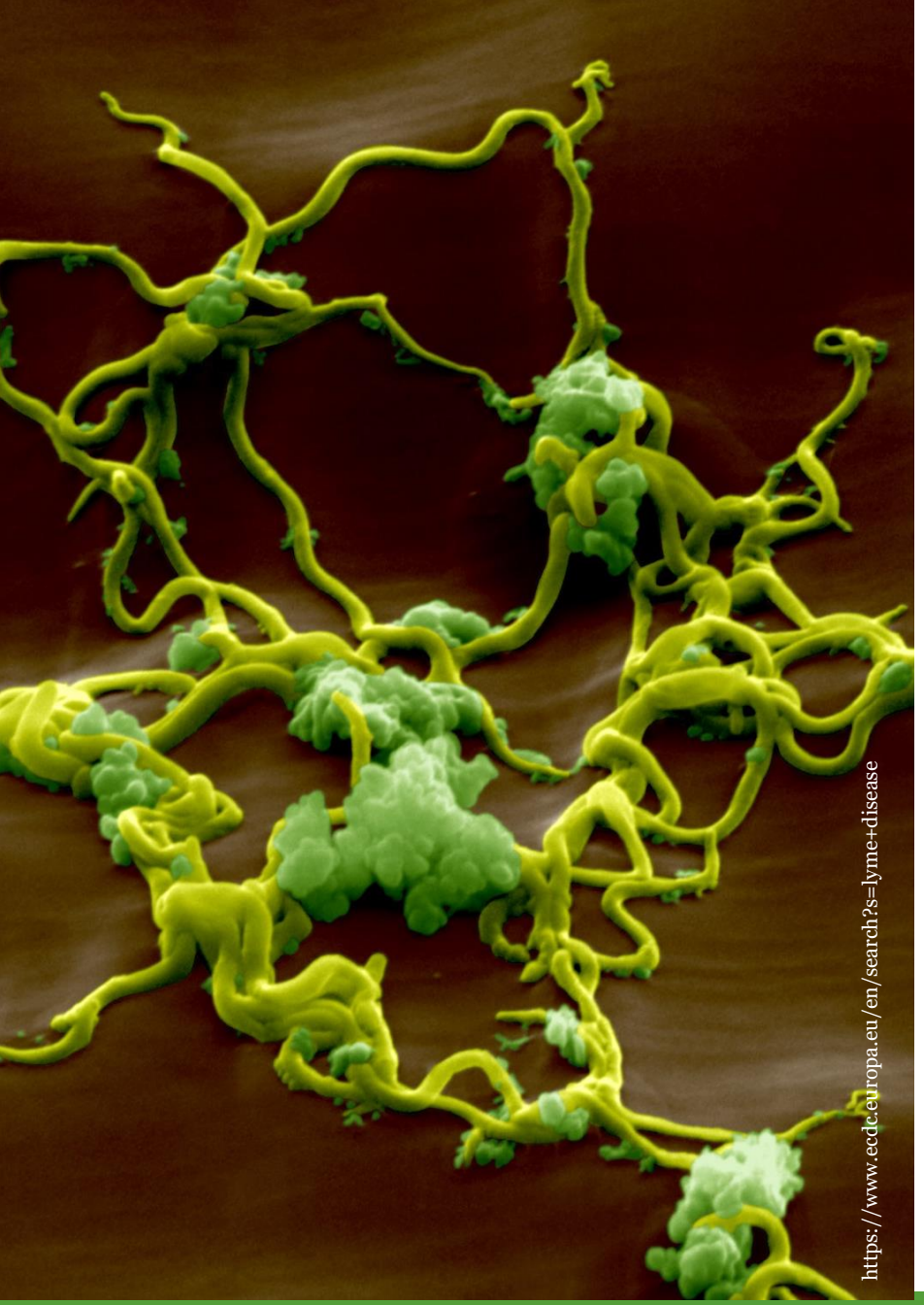
They cannot be resolved one at a time in a linear fashion because each issue causes several issues downstream

Proprietary image created by Myriah Hinchey, 2023

Inflammation: the Driving Force

- Feeds spirochetes
- Causes a majority of symptoms
- Causes an imbalance in the immune system
- Stresses organs
- Imbalances hormones
- Imbalances neurotransmitters and lead to emotional/ cognitive issues
- Causes breakdown of the Gut and increases permeability

Proprietary image created by Myriah Hinchey, 2023



Pearls

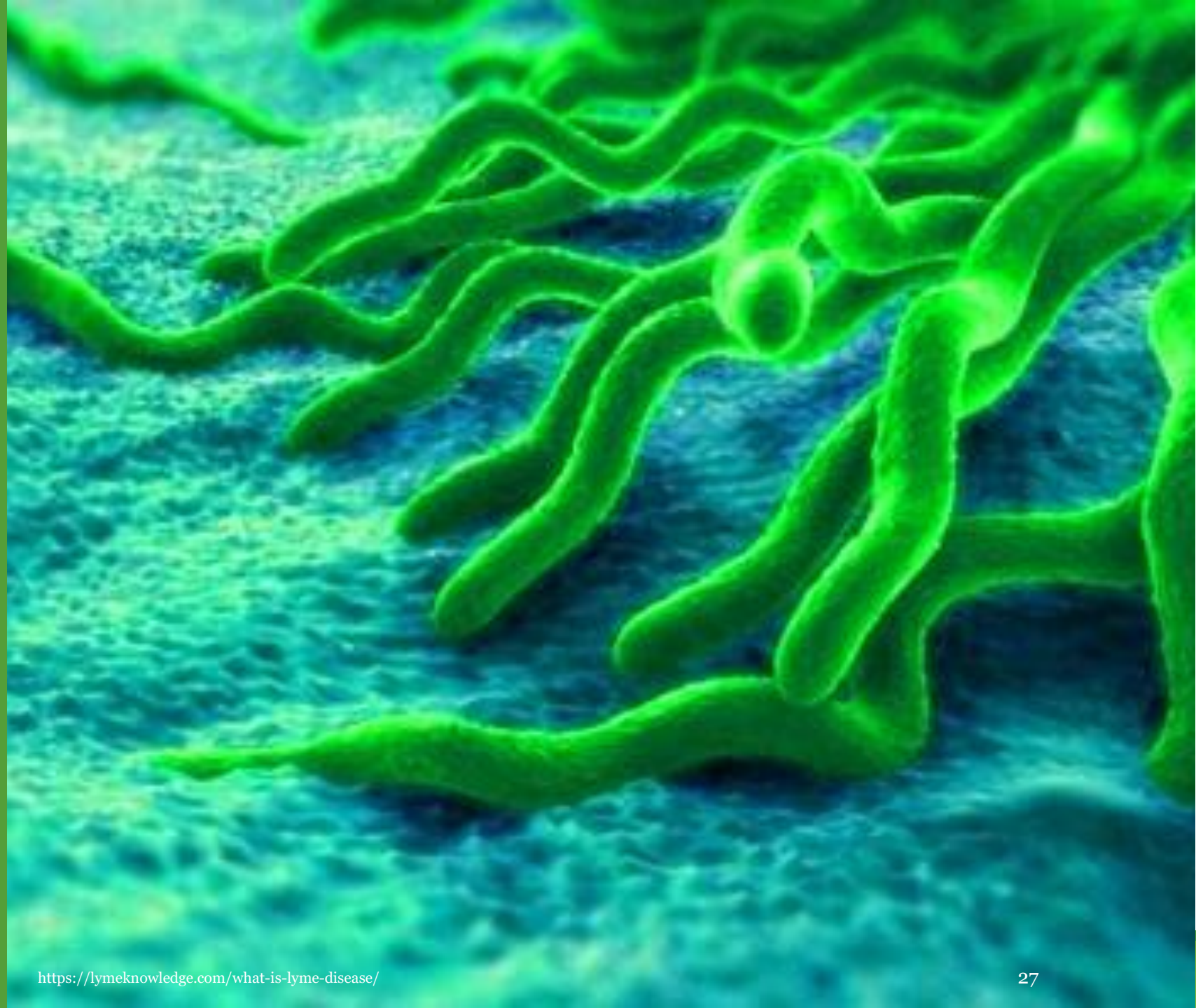
- Lyme is an inflammatory infection: it causes inflammation and lives off the byproducts of it
- Lyme plays on an individual's weaknesses: it finds genetic vulnerabilities and previous injuries
- Severe trauma (mental or physical) can bring dormant infections out
- Any hit to the immune system can cause a reactivation of the infection

https://nypost.com/2019/07/01/woman-claims-lone-star-tick-bite-caused-severe-meat-allergy/

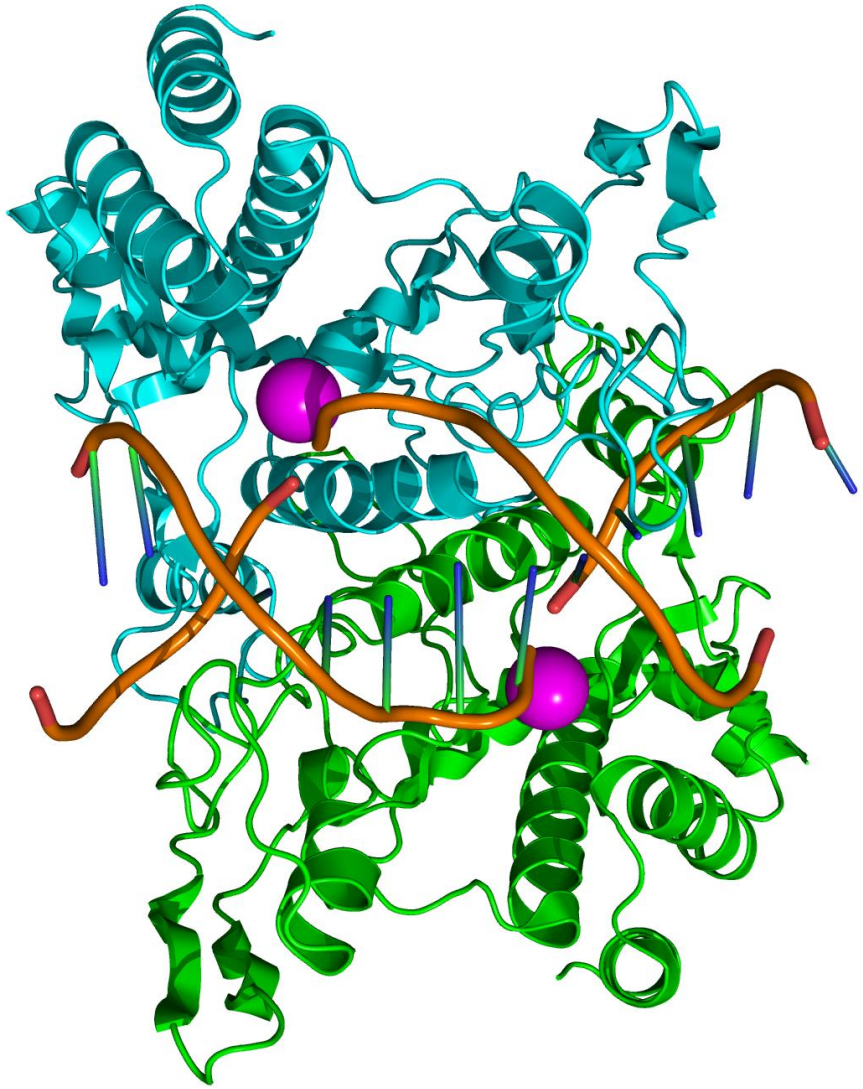
Understanding the Pathophysiology of Lyme

Initial Stages of *Borrelia spp*. Infection

- Adhesion of spirochete to endothelial cells on blood vessel wall via adhesins on spirochete body (Antonara, 2011).
- Spirochetes release cytokines to loosen the Endothelial Cell (EC) junctions— to allow entry to the ECM (Grab, 2005)



https://lymeknowledge.com/what-is-lyme-disease/



Enzymes & Cytokines that Break Down ECM

Hyaluronidase (HYL)

- Hyaluronic Acid (HA) is GAG widely distributed throughout the connective, epithelial and neural tissue
- Major component of Synovial fluid and ECM
- Hyaluronidase (HYL): allows for degradation of Hyaluronic Acid --loosens the CT matrix and EC junctions
- Stopping HYL stops bacteria movement in body (Kolar, 2015)

HYL inhibitors:

- ***Echinacea angustifolia***, which strengthens mucous membranes and skin (Yotsawimonwat, 2010)
- ***Withania somnifera*** (Machiah, 2006)

Aggrecanase

- Aggrecan is a proteoglycan found in ECM and cartilage (Watanabe, 1998) found most abundantly in cartilage of joints
- Spirochetes release aggrecanase to break down aggrecan, releasing nutrients to feed (Russell, 2013)

Aggrecanase Inhibitor:

- ***Polygonum cuspidatum* root** (Bushra, 2021)

Matrix Metalloproteinases (MMPs)

- aka Collagenases
- Degrade the ECM by breakdown of collagen in the body, GAG release (Van Doren, 2015)
- Wide range of pathologies but are extremely damaging to the brain and CNS

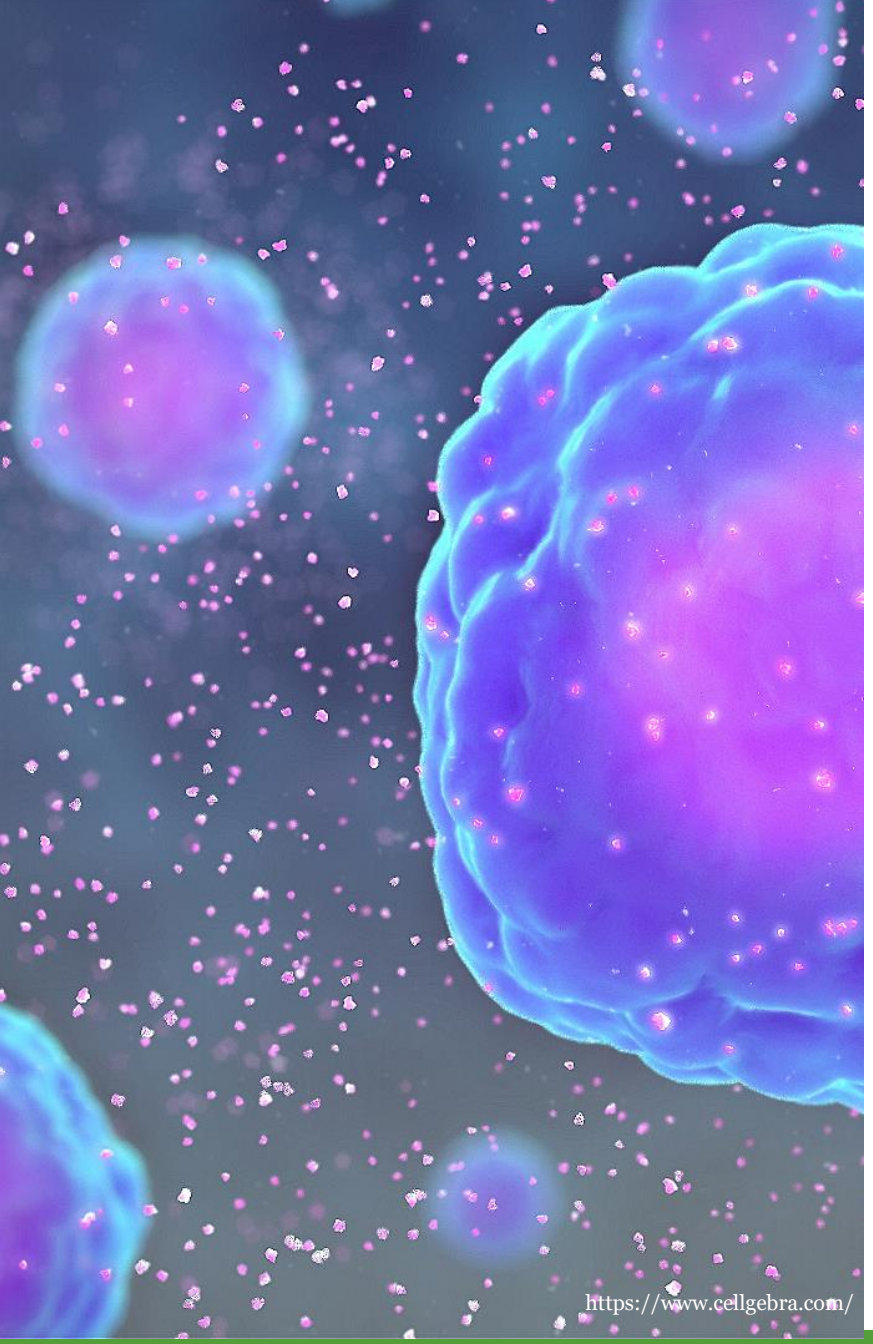
MMPs -1 & 3 Inhibitor:

- ***Polygonum cuspidatum* root** (Kang, 2018)

MMP-9 Inhibitors:

- **Cordyceps** (Cai, 2018), **NAC** (Liu, 2017)
- ***Salvia miltiorrhiza*** (Kim, 2017)
- ***Scutellaria baicalensis*** (Chen, 2014)

Note: Inhibitors halt infection. If spirochetes cannot break down collagen, they cannot feed, reproduce, or spread



Specific Cytokines Affected by TBDs

Flagellin

- Inflammatory protein on flagella that **activates NF-kB** from endothelial cells (Benedikz, 2019)

NF-kB

- Causes immune and inflammatory responses
- Borrelia uses **NF-kB** to further enhance inflammation and immune cell proliferation to break down tissues they need to feed from (Parthasarathy, 2014)

NF-kB inhibitors:

- ***Astragalus*** *(Dong, 2020)*
- **Cordyceps** *(Park, 2018)*
- ***Eupatorium perfoliatum*** *(Shin, 2018)*
- ***Houttuynia cordata*** *(Lee, 2013)*
- ***Polygonum cuspidatum*** *(Park 2017)*
- ***Pueraria lobate*** *(Bulugonda, 2017)*
- ***Salvia miltiorrhiza*** *(Cheung, 2013)*
- ***Scutellaria baicalensis*** *(Li, 2016)*
- ***Withania somnifera*** *(Singh, 2007)*
- **Curcumin** *(Edwards et al., 2020; Shrestha et al., 2017; Xu & Liu, 2017)*

Mitogen-Activated Protein Kinases (MAPKs)

- **Released by stimulation of bacteria (Sahay, 2018)**
- **Primary pathways used to enter a new host - stimulate the cytokine cascade**
  - ERKs: cause issues with: integrity of endothelial barriers, cardiac function, and neural structures in brain (Collins, 2005)
  - JNKs (Johnson, 2002)
  - p38 kinases
- **Upregulation activates proinflammatory cytokines IL-6, TNF-alpha, IL-1B (Johnson, 2023)**

ERK inhibitors: ***Cordyceps sinensis*** (Han, 2010), (Xie, 2014), ***Pueraria lobate*** (Kim, 2017)

JNK inhibitors: ***Cordyceps sinensis*** (Han, 2010), ***Scutellaria baicalensis*** (Huang, 2014)

P38 MAPK inhibitors: ***Cordyceps sinensis*** (Das, 2021), ***Polygonum cuspidatum*** (Kim, 2013), ***Scutellaria baicalensis*** (Zhang, 2017)

IL-6

- Drives fever and multi organ injury
- Multifunctional cytokine that regulates immune system inflammatory response (acute and chronic), and hematopoiesis and cancer growth
- Promotes increase in CD4, IL21, CD8, activation of B cells, VEGF, fibrinogen
- Inhibits T reg cell production (Potere, 2021)
- Crosses BBB stimulates PGE2 in hypothalamus altering body's temp regulation process (Egecioglu, 2018)
- Affects HTH/PIT/AD axis (Späth-Schwalbe, 1994)
- Degeneration of neurons in peripheral and CNS, common in MS, Alzheimer's, depression, etc. (Kimura, 2010)

IL-6 Inhibitors:

Andrographis paniculata (Li, 2021), ***Pueraria lobata*** (Shukla, 2018), ***Salvia miltiorrhiza*** (Jang, 2003), ***Scutellaria baicalensis*** (Liu, 2019)

IL-8

- Primary cause of inflammation and cellular damage resulting from it in *Borrelia spp*. infection (Grygorczuk, 2004)

IL-8 Inhibitors:

- ***Cordyceps sinensis*** (Das, 2021)
- **NAC** (Zhou, 2021)
- ***Polygonum cuspidatum root*** (Quagliariello et al., 2021)
- **Curcumin** (Allijn et al., 2016)
- **Quercetin** (Wu et al., 2015)

IL-1B

- Primary cytokine expressed in *Borrelia spp.* infection (Miller, 1992)
- Stimulates cell proliferation and increases COX2 in CNS (Molina-Holgado, 2000)
- Increased sensitivity to pain (Simon, 1999)
- Plays a multifaceted role in acute & chronic conditions

ACUTE

- Is a potent pro-inflammatory cytokine crucial for host-defense response to injury and infection
- Plays a beneficial role in resolving ACUTE inflammation

CHRONIC

- Is an immune amplifier of immune reactions and leads to autoimmune and autoinflammatory diseases
- Supports tumor development, growth and metastasis. (Mardi, 2021)

IL-1B Inhibitors:

Cordyceps sinensis (Hu, 2014), ***Eupatorium perfoliatum*** (Chen, 2018), ***Polygonum cuspidatum*** (Liu, 2018), ***Pueraria lobata*** (Zhu, 2014), ***Salvia miltiorrhiza*** (Ma, 2016), ***Scutellaria baicalensis*** (Hsieh, 2007)

TNF-alpha

- Pro-inflammatory cytokine produced by many cell types in response to inflammation, infection, and environmental stress
- Signals cell proliferation, apoptosis, modulation of immune response, and induction of inflammation (Karki, 2021)
- Elevated in many chronic inflammatory conditions
- Affects HTH/PIT/AD axis (Dunn, 2000)
- Causes issues with appetite, body temperature, liver function, insulin resistance (Knobler, 2005)
- Causes severe brain and CNS damage (Raffaele, 2020)

TNF-a Inhibitors:

Cordyceps sinensis (Zhu, 2012), ***Eupatorium perfoliatum*** (Chakravarti, 2011), ***Houttuynia cordata*** (Park, 2005), ***Scutellaria baicalensis*** (Wu, 2020), ***Salvia miltiorrhiza*** (Peng, 2007)

INF-alpha

- Causes tissue inflammation, organ damage, autoimmune conditions, fever, fatigue, and leukopenia, and depression (by stimulating IDO or indoleamine 2,3 dioxygenase) (Wicher, 2005)

IFN-a Inhibitors:

- ***Polygonum cuspidatum*** (Lin, 2015)
- ***Salvia miltiorrhiza*** (Zhang, 2012)
- ***Scutellaria baicalensis*** (Błach-Olszewska, 2008)

Indoleamine 2,3 dioxygenase (IDO)

- Enzyme that breaks apart L-tryptophan into:
  - 3- HK (3-hydroxykynurenine)
  - QUIN (quinolinic acid)
  - KYNA (kynurenic acid)
- Decreases T cells
- Severely decreases melatonin and serotonin

IDO inhibitors:

- ***Scutellaria baicalensis*** (Chen, 2012)
- ***Crinum latifolium*** (Jenny, 2011)

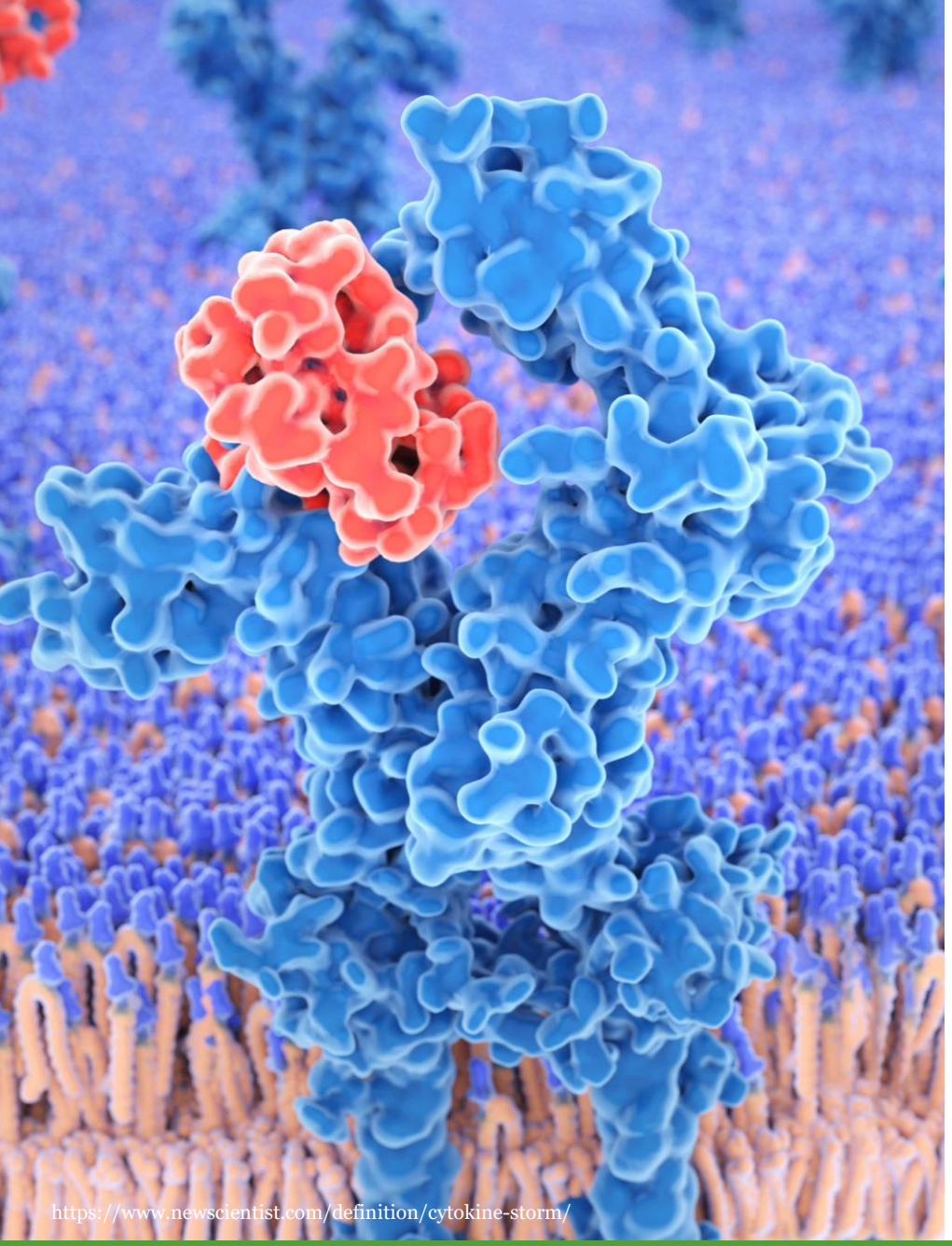
QUIN

- Causes overstimulation of the neurons in brain, excitotoxicity lesions, degradation of brain tissue, ROS and sometimes seizures (Heyes, 1992)
- The number and seriousness of seizures people experience is directly related to levels of QUIN and 3-HK (Basile, 1995)

QUIN Inhibitors:

- ***Uncaria rhynchophylla*** (Buhner, 2015)
- ***Scutellaria baicalensis*** (Buhner, 2015)
- **Melatonin** (Vega-Naredo, 2005)
- **Selenium** (Santamaria, 2003)

NOTE:* Scutellaria *contains high levels of melatonin, which decreases brain's vulnerability to Lyme infection, is protective of brain structures, and increases sleep.



https://www.newscientist.com/definition/cytokine-storm/

This ongoing inflammatory cytokine cascade leads to an imbalance in the immune system.

THE POWER OF 3 HERBS:

1. ***Polygonum cuspidatum*** **(Japanese knotweed)**
2. ***Scutellaria baicalensis*** **(Chinese skullcap)**
3. ***Withania somnifera*** **(Ashwagandha)**

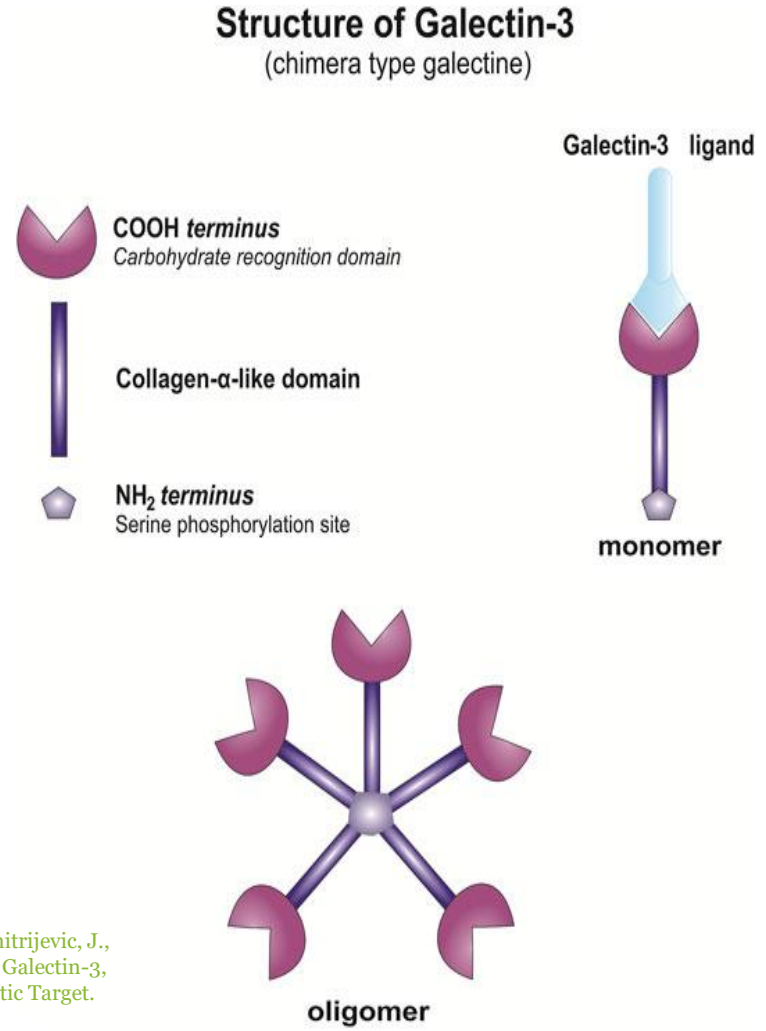
- ✓ Inhibit enzymes that degrade collagen, ECM, & endothelial cells (Bushra, 2021; Chen, 2014; Kang, 2018; Machiah, 2006;)
- ✓ Inhibit inflammatory cytokine cascade

(Blach-Olszewska, 2008; Chen, 2012; Hsich, 2007; Kim, 2013; Li, 2016; Lin, 2019; Liu, 2018; Park, 2017; Quagliariello et al., 2021; Wu, 2020; Zhang, 2017)

- ✓ Balance the immune system (Bani et al., 2016)

Additional Upstream Driver of Inflammation

- **Galectin-3 (gal-3)** is a β-galactoside-binding protein which regulates cell–cell and cell–extracellular matrix interactions affecting cell proliferation, migration, adhesion, differentiation and apoptosis
- Produced by macrophages, monocytes, dendritic cells (DCs), eosinophils, mast cells, NK cells, and activated T and B cells
- During the past decade, gal-3 has attracted the attention of researchers due to its regulatory role in immune response, inflammation, and fibrosis



Velickovic, M., Arsenijevic, A., Acovic, A., Arsenijevic, D., Milovanovic, J., Dimitrijevic, J., Todorovic, Z., Milovanovic, M., Kanjevac, T., & Arsenijevic, N. (2021). (2021). Galectin-3, Possible Role in Pathogenesis of Periodontal Diseases and Potential Therapeutic Target. Frontiers in Pharmacology, 12. https://doi.org/10.3389/fphar.2021.638258

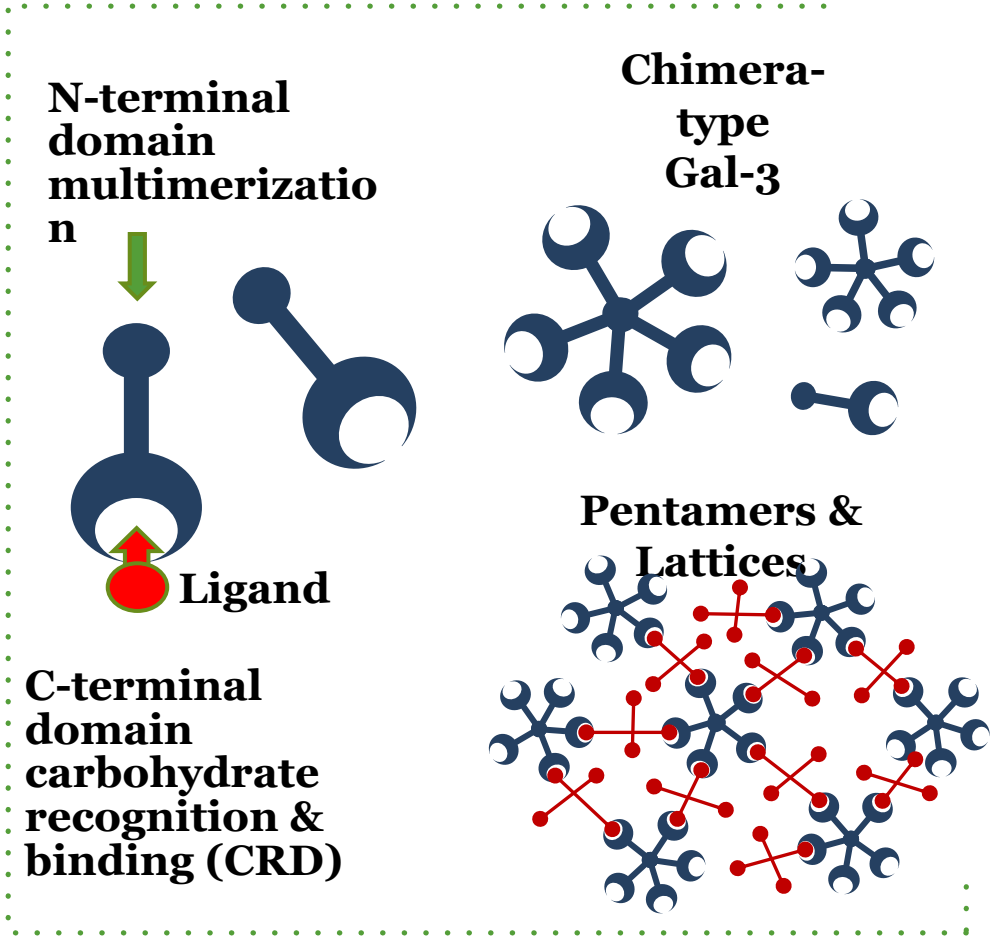
Gal-3: Multifunctional Mediator in Inflammation

(Diaz-Alvarez, 2017)

- **Activates *Initial*** immune response to acute infection
- **Orchestrates** recruitment and infiltration of immune cells to sites of infection
- **Initiates** pro-inflammatory signaling cascades to fight infection

Gal-3 is an "**Alarmin**"

Responds *Immediately* in Injury or Infection



https://ir.galecto.com/static-files/4c842494-898c-41ea-b1cc-e53de49e6d50

Gal-3 Promotes Establishment of Borrelia and Other Pathogenic Biofilms

Acute Infection: Gal-3 plays an important role as an “alarmin”, immediately activating an initial immune response by mobilizing recruitment and infiltration of immune cells to sites of infection and stimulating immune cell production of inflammatory cytokines to combat infection.

Chronic Infection: Gal-3 is like an alarm that never turns off, continuing to drive inflammatory, adhesive, profibrotic and proliferative pathways that promote systemic inflammation and immune suppression. Gal-3 prevents immune surveillance by crosslinking T-cell receptors and CD45 by binding glycans. It suppresses adequate immune responses by blocking T-cell receptor activity, downregulating T-cell signaling and inhibiting dendritic, T-cell and Natural Killer (NK) cell function.

Díaz-Alvarez L, Ortega E. The Many Roles of Galectin-3, a Multifaceted Molecule, in Innate Immune Responses against Pathogens. Mediators Inflamm. 2017;2017:9247574.
Wolfert MA, Boons GJ. Adaptive immune activation: glycosylation does matter. Nat Chem Biol. 2013 Dec;9(12):776-84.

Galectin-3: a Multifaceted Molecule

Inflammatory Response & Immune Health

When the galectin-3 alarm doesn't turn off, inflammation becomes chronic and immune dysregulation occurs:

- Autoimmune diseases
- Suppressed immunity
- Cytokine storms
- Mast cell activation

Galectin-3 also:

- Promotes pathogen adhesion and evasion
- Forms biofilms
- Upregulates MMP-9

Díaz-Alvarez L, Ortega E. The Many Roles of Galectin-3, a Multifaceted Molecule, in Innate Immune Responses against Pathogens. Mediators Inflamm. 2017;2017:9247574.
Wolfert MA, Boons GJ. Adaptive immune activation: glycosylation does matter. Nat Chem Biol. 2013 Dec;9(12):776-84.

GAL-3 Fuels the Cytokine Storm & MCA

Excessive cytokine profile /
Hyper- inflammation
IL-1β, IL-2, IL-6, IL-17, IL-8, TNF,
CCL2, MCP-1

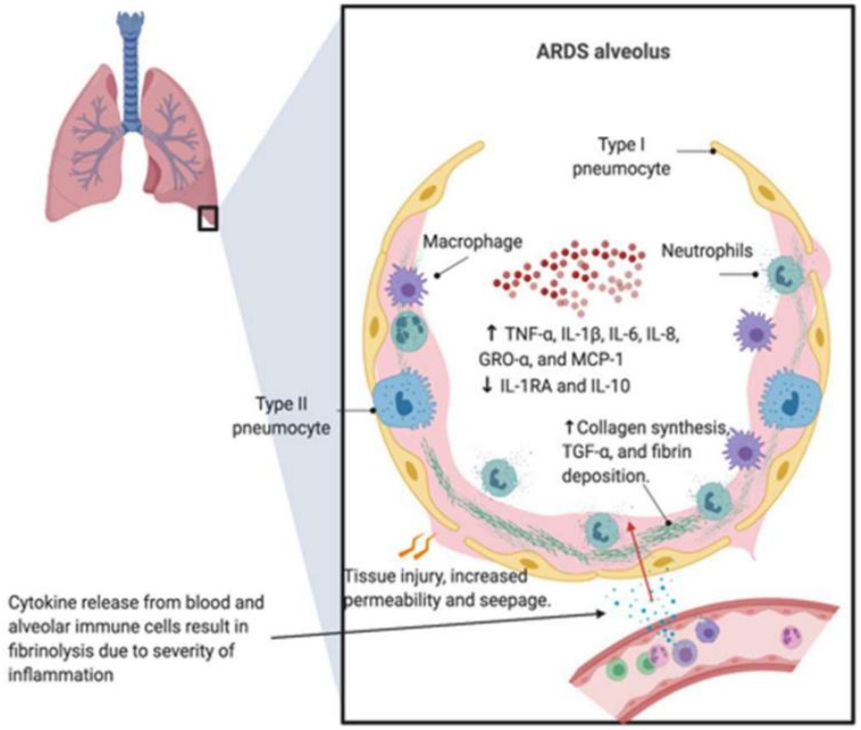
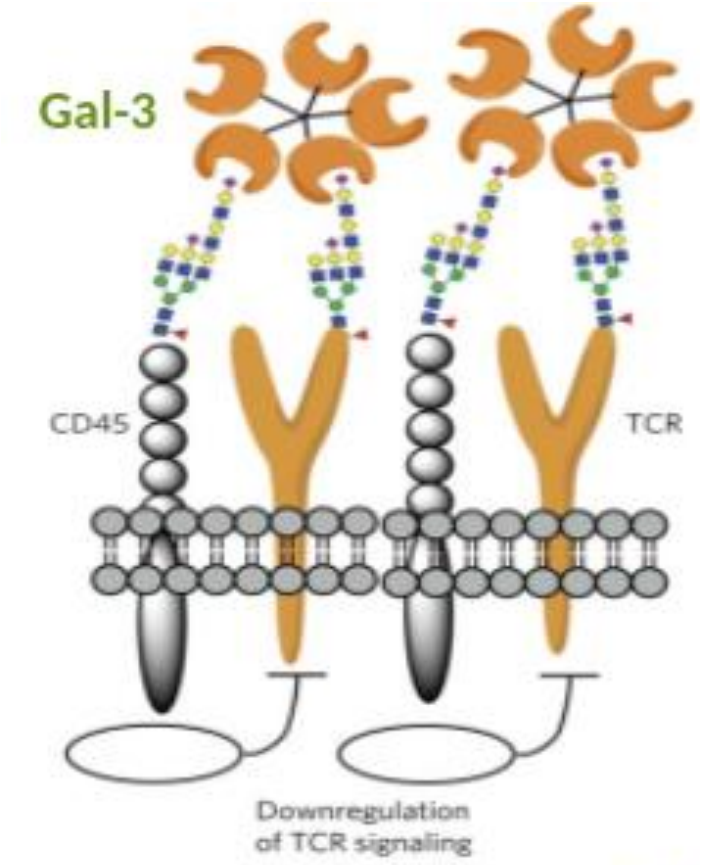


Image: O'Regan, Anthony, et al. *Interleukin-6 Use in COVID-19 Pneumonia Related Macrophage Activation Syndrome*. 2020. *DOI.org (Datacite)*, https://doi.org/10.13140/RG.2.2.36718.15681.

- Fuels the Cytokine Storm in Infections & Inflammation
- Promotes Mast Cell Activation
- In the vast amount of scientific research, the primary cytokines recognized as being upregulated by Gal-3 in sepsis and infections are:
  - Chemokine ligand 6 (CXC-6; also known as granulocyte chemotactic protein 2)
  - Interferon-γ, Interferon γ-induced protein 10
  - TNF-α, NF-κB, MCP-1
  - Interleukin-1β (IL-1β), IL-1α, IL-6, IL-8, IL-17

Díaz-Alvarez L, Ortega E. The Many Roles of Galectin-3, a Multifaceted Molecule, in Innate Immune Responses against Pathogens. Mediators Inflamm. 2017;2017:9247574.
Wolfert MA, Boons GJ. Adaptive immune activation: glycosylation does matter. Nat Chem Biol. 2013 Dec;9(12):776-84.

GAL-3 Modulates Immune Reactivity in Chronic Illness



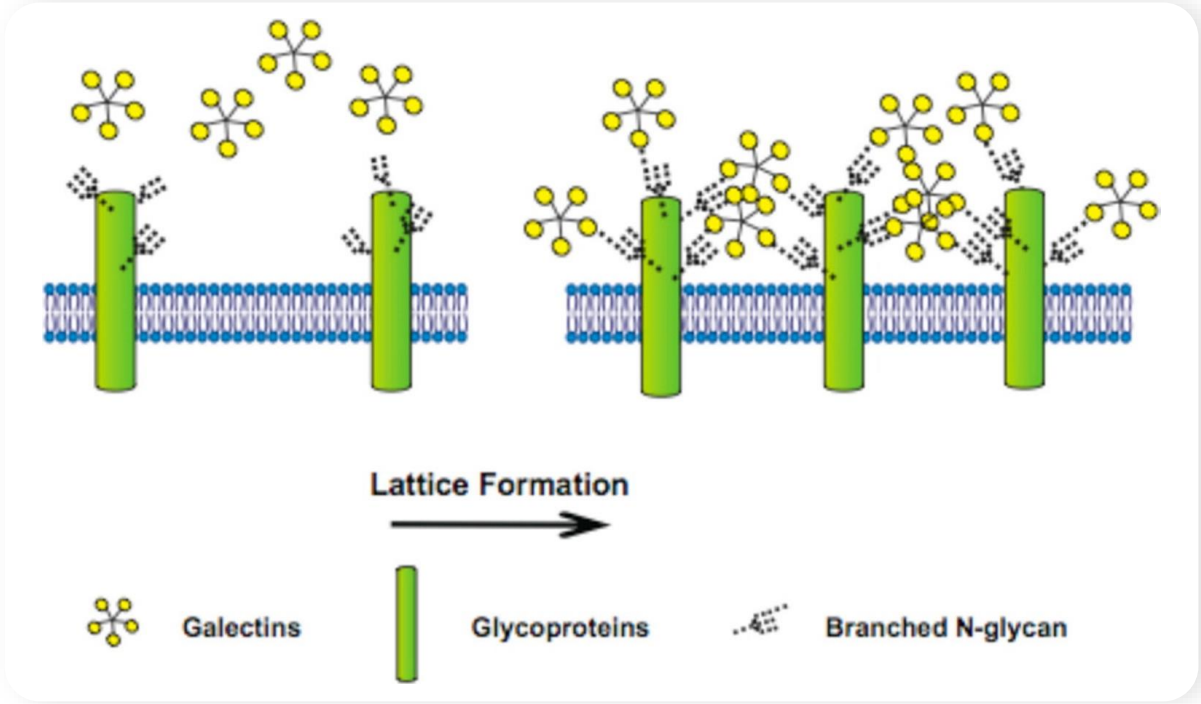
- Gal-3 crosslinks T-cell receptors & CD45 by binding glycans
- Suppresses immune surveillance
- Blocks T-cell receptor activity
- Downregulates T-cell signaling
- Inhibits dendritic, T cell, & NK cell function

Wolfert, Margreet A., and Geert-Jan Boons. "Adaptive Immune Activation: Glycosylation Does Matter." *Nature Chemical Biology*, vol. 9, no. 12, Dec. 2013, pp. 776–84. *DOI.org (Crossref)*, https://doi.org/10.1038/nchembio.1403.

Díaz-Alvarez L, Ortega E. The Many Roles of Galectin-3, a Multifaceted Molecule, in Innate Immune Responses against Pathogens. Mediators Inflamm. 2017;2017:9247574.
Wolfert MA, Boons GJ. Adaptive immune activation: glycosylation does matter. Nat Chem Biol. 2013 Dec;9(12):776-84.

The Galectin-3 Lattice

Promotes the Establishment of Biofilms



Gal-3 Lattice

A dynamic, extracellular, planar gel-like polymer formed by crosslinking with surface glycoproteins and glycolipids

Nabi IR, et al. The galectin lattice at a glance. *J Cell Sci.* 2015 Jul 1;128(13):2213-9.
Chiu CG, et al. *Am J Pathol.* 2010 May;176(5):2067-81.

Gal-3-Enhanced Biofilms Also Affect the Gut Microbiome

Promotes infection and invasion of harmful microbes

Elevated Gal-3
Expression in epithelial gut lining

Gal-3 binds to pathogenic bacteria, viruses, fungi and parasites, allowing for tissue adhesion and immune evasion

Pathogens able to exploit Gal-3, augment their capacity to colonize and survive within host environment

Kavanaugh D, Kane M, Joshi L, Hickey RM. Detection of galectin-3 interaction with commensal bacteria. Appl Environ Microbiol. 2013 Jun;79(11):3507-10.

Gal-3 Promotes GI Inflammation

- Gal-3 is upregulated in a compromised intestinal epithelium, and binds to pathogenic bacteria, viruses, fungi, and parasites, allowing for tissue adhesion & immune evasion.

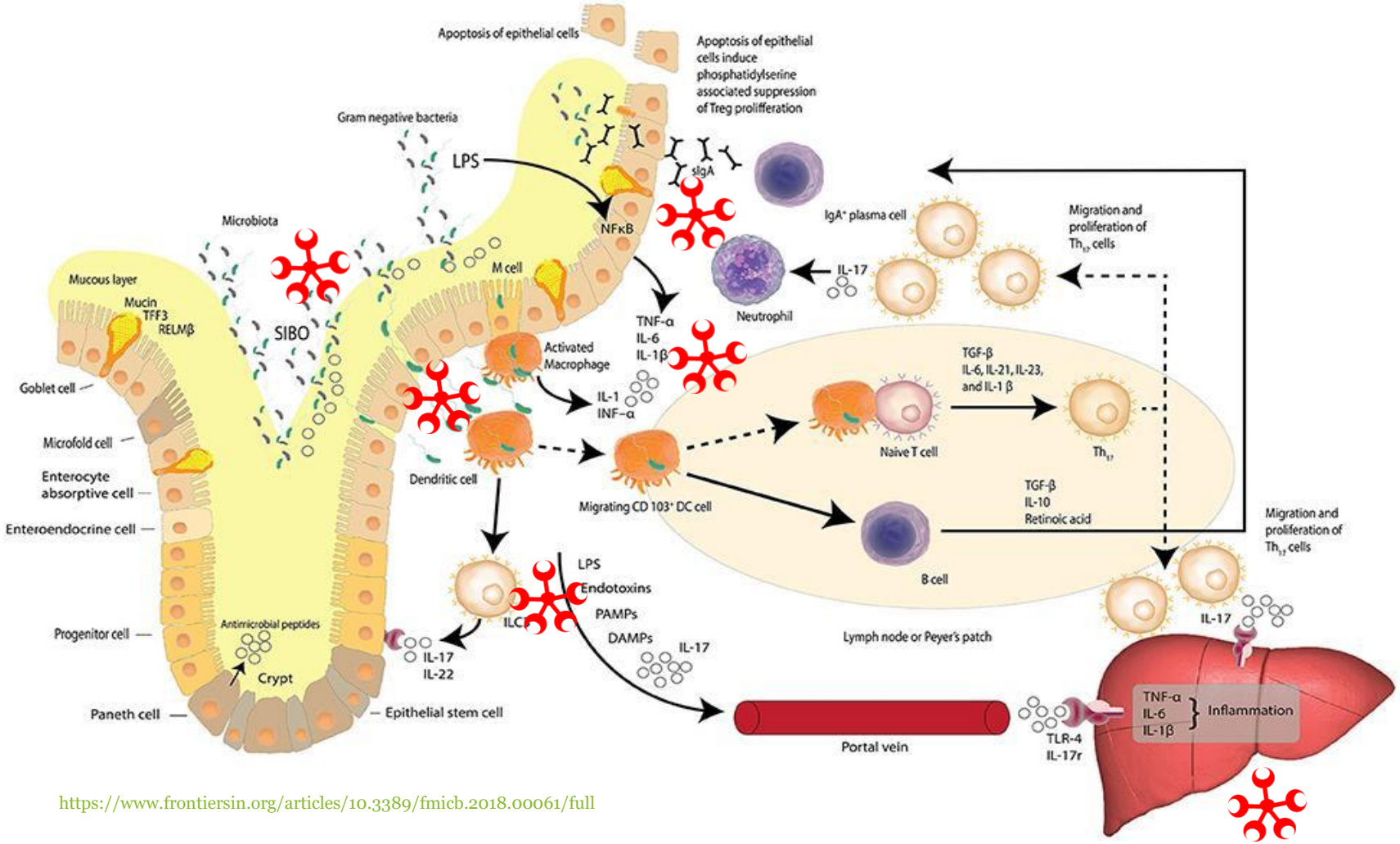
- Compromised tight junctions allow for translocation of pathogens, immunogenic food particles, and endotoxins. Gal-3 also promotes reactive immune upregulation to these foreign particles, leading to systemic inflammation, neuroinflammatory symptoms, and intensifying of Herxheimer reactions.

Yu TB, Dodd S, Yu LG, Subramanian S. Serum galectins as potential biomarkers of inflammatory bowel diseases. PLoS One. 2020 Jan 13;15(1):e0227306.
Frol'ová L, Smetana K Jr, Borovská D, et al. Detection of galectin-3 in patients with inflammatory bowel diseases: new serum marker of active forms of IBD? Inflamm Res. 2009 Aug;58(8):503-12.

Leaky Gut - Systemic Inflammation - Immune Hyperreactivity

(Saltzman, 2018)

Gal-3



https://www.frontiersin.org/articles/10.3389/fmicb.2018.00061/full

Biofilms, Infections and Galectin-3 (Croston, 2020)

Higher gal-3 levels found in:

- Damp building syndrome and other mycotoxin illnesses
- Lungs in people exposed to black mold
- Autoimmune conditions

Drives:

- Cytokine storm, mast cell activation, Herxheimer reactions
- Dysbiosis and biofilms
- MMP9 elevation and breakdown of gut wall / blood brain barrier

As the most-researched Galectin-3 blocker, MCP attenuates these effects

Croston TL, Lemons AR, Barnes MA, Goldsmith WT, Orandle MS, Nayak AP, Germolec DR, Green BJ, Beezhold DH. Inhalation of *Stachybotrys chartarum* Fragments Induces Pulmonary Arterial Remodeling. Am J Respir Cell Mol Biol. 2020 May;62(5):563-576.
Teirilä L, Karvala K, Ahonen N, Riska H, Pietinalho A, Tuominen P, Piirilä P, Puustinen A, Wolff H. Proteomic changes of alveolar lining fluid in illnesses associated with exposure to inhaled non-infectious microbial particles. PLoS One. 2014 Jul 17;9(7):e102624.

Biofilms, Infections and Galectin-3: Summary

- Galectin-3 forms backbone "scaffolding" for biofilm structures
- Promotes adhesion of pathogenic microbes to epithelial tissues
- Shields pathogens from immune surveillance and drug therapies
- Drives cycle of dysbiosis to systemic inflammation

https://www.thetimes.co.uk/article/yoga-could-reduce-risk-of-cancer-relapse-say-scientists-b5dpbff9q

A Holistic Plan of Care

Naturopathic whole-body approach

Healing the patient by correcting immune system dysfunction, decreasing inflammation, and ultimately making them inhospitable to the infections

Making the body inhospitable to the infection while shrinking the bacterial/ parasitic load will give the best chance for eradicating the infections, healing the body, and restoring proper function.

Dr. Hinchey's 10B Approach:

Core Principles for Healing TBD

10 Goals for Successful Resolution of Lyme

A Comprehensive Approach to Treat TBD:

I. Background Check
II. Bandaids
III. Block Inflammation – (3 part)
IV. Buffer ANS
V. Balance Immune system
VI. Build Gut
VII. Break Down Biofilms
VIII. Bolster Detoxification
IX. Bind Toxins (Herx)
X. Blast Bugs

BACKGROUND CHECK

Investigate all of the things that fill the patient's "bucket", causing them to become hospitable to the infection(s):

- Micronutrient deficiencies (Calder, 2020)
- Dysfunctional digestion / malabsorption (Mullin et al., 2014)
- Food sensitivities and inflammatory and toxic food intake (gluten, dairy, sugar, processed foods etc.) (Fasano, 2012)
- Rx intake affecting nutrient status and burdening detoxification pathways (Liska et al., 2006)
- Hormone dysregulation (Aranow, 2011)
- Mindset and perceptions (Dhabhar, 2014)
- Mental, emotional, and physical stressors, and HPA axis dysregulation (McEwen, 2006)
- Sleep and circadian rhythm dysregulation (Besedovsky et al., 2019)
- Sedentary lifestyle, inactivity (Nieman, 2019)
- Poor social network, lack of community and healthy interpersonal relationships (Uchino, 2004)
- Biotoxins (mold), environmental chemicals, toxins in food, air, water (Shoemaker & House, 2006)

BANDAIDS

Enlisting a variety of therapeutic interventions to minimize symptoms and alleviate ongoing stress response to promote PNS function and healing, while simultaneously uncovering and treating the underlying root causes:

- **Adaptogenic Herbs:** Rhodiola rosea, Ashwagandha, Holy Basil, and Eleuthero (Panossian & Wikman, 2010)
- **Anti-inflammatories:** Both pharmaceutical and natural agents (Serhan & Savill, 2005)
  - LDN (Low-Dose Naltrexone): Modulates the immune system and reduces inflammation (Younger et al., 2018)
  - Phosphatidylserine: Helpful in lowering elevated cortisol levels (Benton et al., 2001)
  - Magnesium: the "relaxation mineral", supports nervous system function (Sartori et al., 2012)
  - Vitamin C: Required for cortisol production (Patak et al., 2004)
  - B Vitamins: Essential for energy production and neurotransmitter synthesis (Kennedy, 2016)
  - Omega-3 Fatty Acids: anti-inflammatory and support brain function (Bradbury, 2011)
  - L-Theanine: Promotes a calm, relaxed state (Nobre et al., 2008)
  - Curcumin: Has potent anti-inflammatory and antioxidant properties (Hewlings & Kalman, 2017)
- **Repleting Nutrients:** Ensuring optimal levels for physiological function through food and nutraceuticals
- **Adequate Sleep and sleep aids:** proper sleep hygiene, essential for detoxification & repair (Riemann & Baglioni, 2012)
- **Limiting Stimulants:** Such as caffeine and nicotine (Rogers et al., 2013)
- **Therapeutic Technologies:** Such as HBOT and PEMF (Thom, 2009; Markov, 2007)
- **Bodywork:** Including cranial sacral therapy and massage (Upledger, 1983; Field et al., 2010)
- **Professional Counseling/Therapy: Psychotherapy** (Otte et al., 2016): Cognitive Behavioral Therapy (Hofmann et al., 2012), Biofeedback (Lehrer et al., 2003), EMDR (Shapiro, 2001)

BLOCK Inflammation

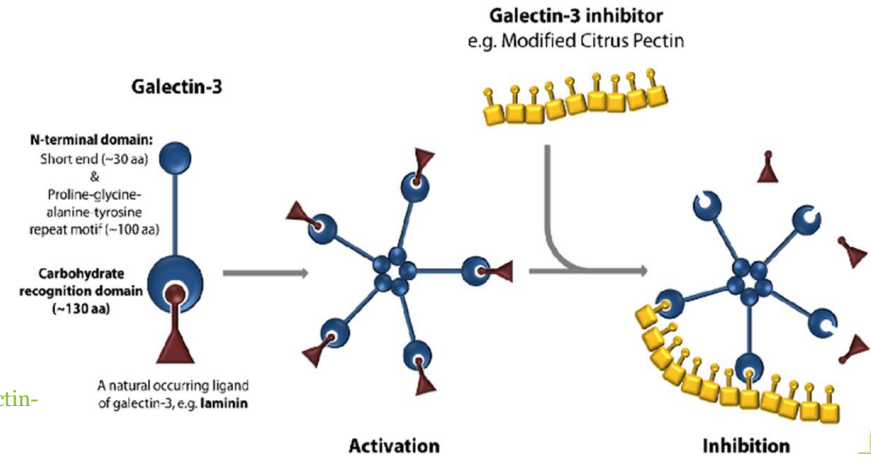
4-part step:

1. Block Galactin-3
2. Block inflammatory cytokine cascade
3. Block inflammatory enzymes
4. Block Inflammatory food, chemicals, toxins, etc

BLOCK Galactin-3

Gal-3 Natural Inhibitor: Modified Citrus Pectin (Xu, 2020)

- Polysaccharide soluble fiber derived from the pith of citrus peels
- Modified to lower molecular weight and esterification for enhanced GI absorption
- Molecular weight <15kDa (unmodified 50-300kDa)
- Esterification <10% (unmodified ~70%)



https://www.researchgate.net/figure/Natural-occurring-ligands-bind-galectin-3-and-cause-galectin-3-activation-Following_fig4_262019249

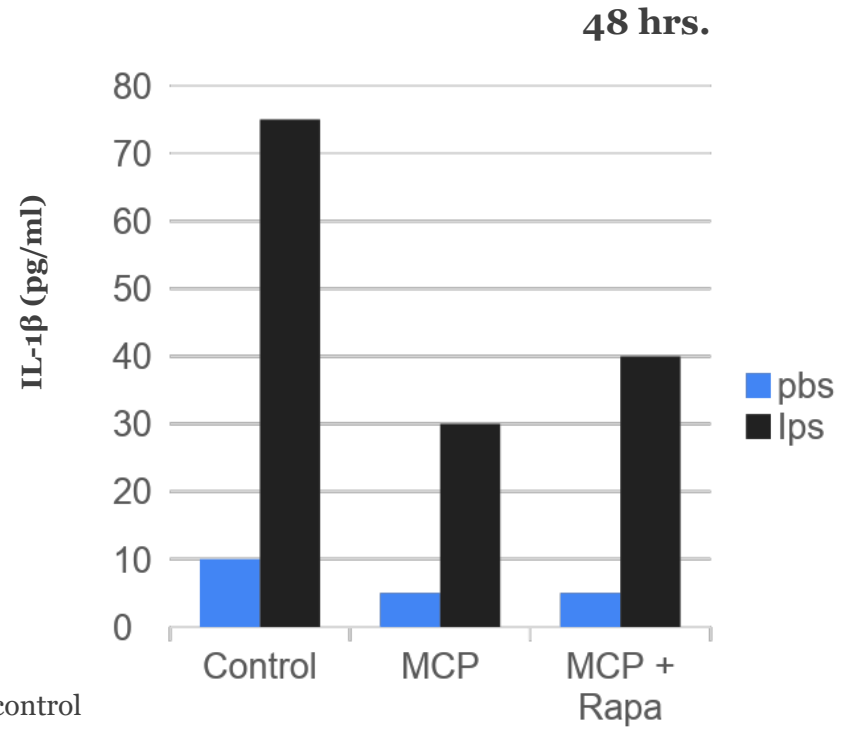
BLOCK Inflammatory Cytokines

Polygonum cuspidatum and ***Scutellaria baicalensis*** together inhibit <u>all</u> of the inflammatory cytokines involved in LD

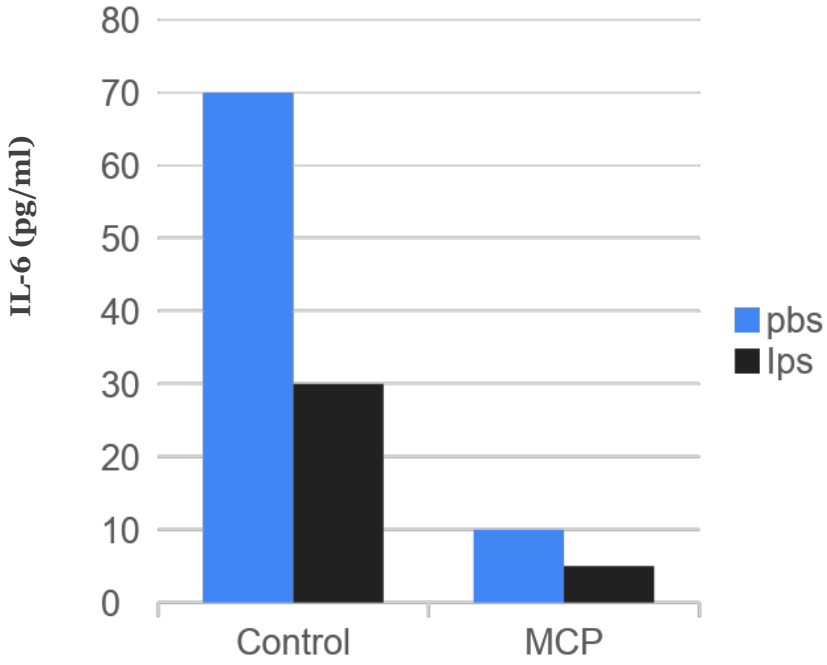
- NF-KB (Park, 2017); (Li,2016)
- IDO (Chen, 2012)
- IL-6 (Lin, 2019)
- IFN-a (Blach-Olszewska, 2008)
- IL-8 (Quagliariello et al., 2021)
- MAPKs (Kim, 2013); (Zhang, 2017)
- IL-1B (Liu, 2018); Hsich, 2007)
- TNF-a (Wu, 2020)

MCP Reduces Proinflammatory Cytokines (Ma, 2016)

In Cultured Microglia Cells treated with LPS

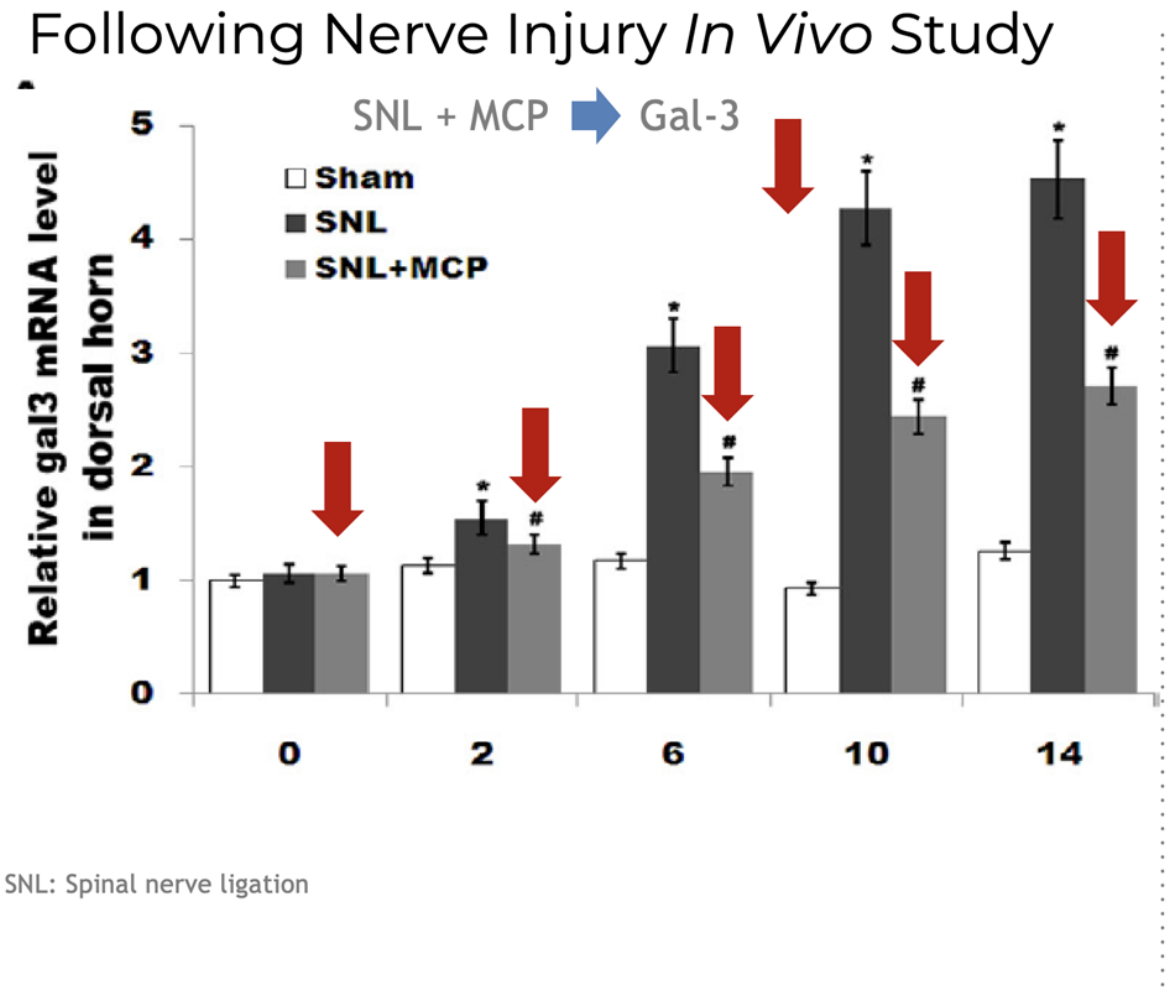


*P<0.05 v control



Results: MCP Reduced Neuropathic Pain in Peripheral Nerve Injury

MCP Reduces Neuroinflammation & Pain (Ma, 2016)



BLOCK Inflammatory Enzymes That Degrade Collagen, ECM, & Endothelial Cells

- **Inhibit Aggrecan**
  - ***Polygonum cuspidatum*** root (Bushra, 2021)

- **Inhibit Hyaluronidase (HYL)**
  - ***Echinacea angustifolia***, which strengthens mucous membranes and skin (Yotsawimonwat, 2010), ***Withania somnifera*** (Machiah, 2006)

- **Inhibit MMPs (collagenases)**
  - ***Polygonum cuspidatum*** (Kang, 2018), **Curcumin** (Zeng et al., 2019; Mun et al., 2009; Zhu et al., 2020; Cao et al., 2015), ***Salvia miltiorrhiza*** (Kim, 2017), ***Scutellaria baicalensis*** (Chen, 2014)

- **Protect endothelial cells Polygonum cuspidatum**

Buffer ANS

- **Lyme has been documented to cause autonomic dysfunction (Carod-Artal, 2018)**
  - Urinary retention and intestinal pseudo-obstruction
- **Improving symptoms of dysautonomia with nutrition and supplementation (Do, 2021)**
  - ✓ Vitamins B1, B12, C, D
  - ✓ MSM + silica
  - ✓ Salt
  - ✓ Pre- and probiotics
  - ✓ IV hydration

IV

Buffer ANS, con't.

- **Dietary interventions:** anti-inflammatory foods that support the microbiome (Aggarwal & Sung, 2009); Quigley, 2013), control blood sugar and reduce inflammation with omega-3 fatty acids (Wall et al., 2010) and probiotics (Cryan & Dinan, 2012), avoid caffeine (Wikoff, et al., 2017), mindful eating (Albers, 2008)
- **Physical activity: Exercise,** Yoga and Tai Chi (Jahnke et al., 2010)
- **Stress Management:** breathing techniques (6), mindfulness meditation (Kabat-Zinn, 2003), biofeedback and HRV (Zucker et al., 2009), creative/art therapy (Stuckey & Nobel, 2010)
- **Sleep Hygiene** (Hirshkowitz et al., 2015)
- **Circadian rhythm balance** (Walker, 2017): getting AM sunlight and avoid PM blue light (Cho et al., 2015)
- **Bodywork:** acupuncture (Lee & Choi, 2013), craniosacral therapy, massage (Upledger, 2002)
- **Grounding or earthing** (Chevalier et al., 2012)
- **Digital detox** and avoidance of EMFs (Twenge & Campbell, 2018)
- **Trauma Therapies:** EMDR, ART, etc. (Shapiro, 2001); (Kip et al., 2012)
- **Community & supportive relationships:** foster connection (Holt-Lunstad et al., 2017); (Uchino, 2006)

BALANCE Immune System

Balance Th1 and T2:

Withania somnifera

- Counteracts the exact modulation of the immune system that tick saliva and protozoa initiate and maintain to keep infection going (Bani et al., 2006).
- Balances Th1 and Th2 (Bani et al., 2006).

Astragalus spp

- Modulates the imbalanced relationship between Th1 and Th2 cytokines (Chen, 2014).

Increase lymphocytes:

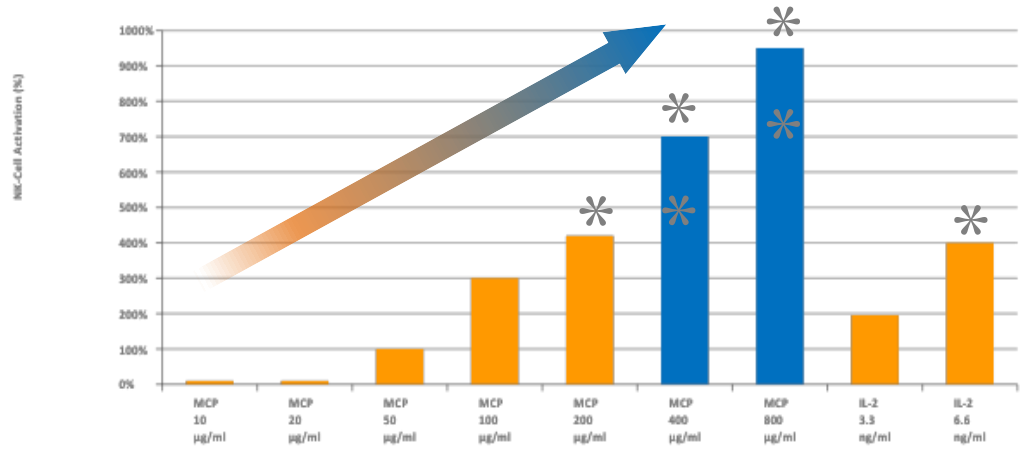
Uncaria tomentosa (Lamm et al., 2001).

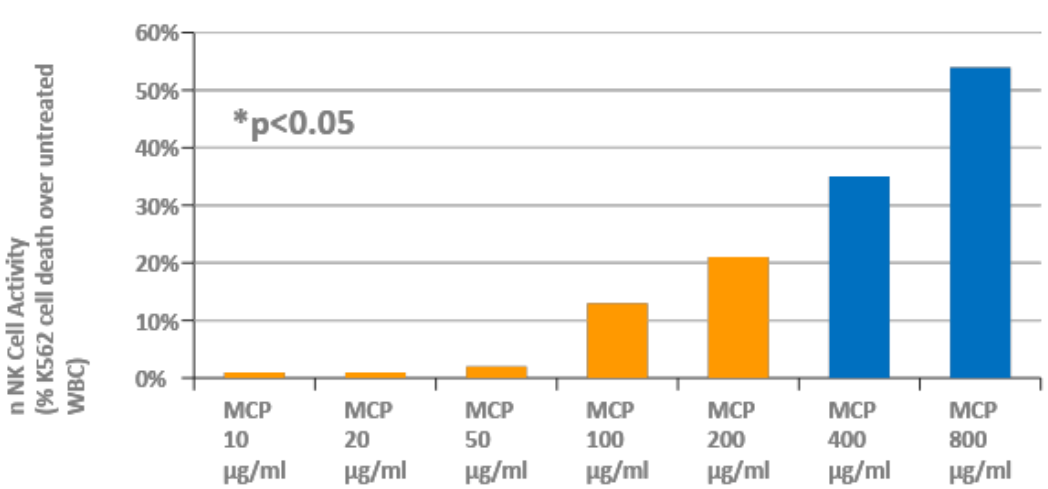
Immune system enhancement:

Echinacea angustifolia (Zhai et al., 2007).

MCP Immuno-Modulatory Properties (Ramachandran, 2011)

Method: MCP treated blood samples analyzed using flow cytometry. Functionality of activated NK Cells tested by incubation with lymphocytes and K562 leukemic cells





MCP Activated:

- T-Cytotoxic cells
- B –Cells
- NK Cells

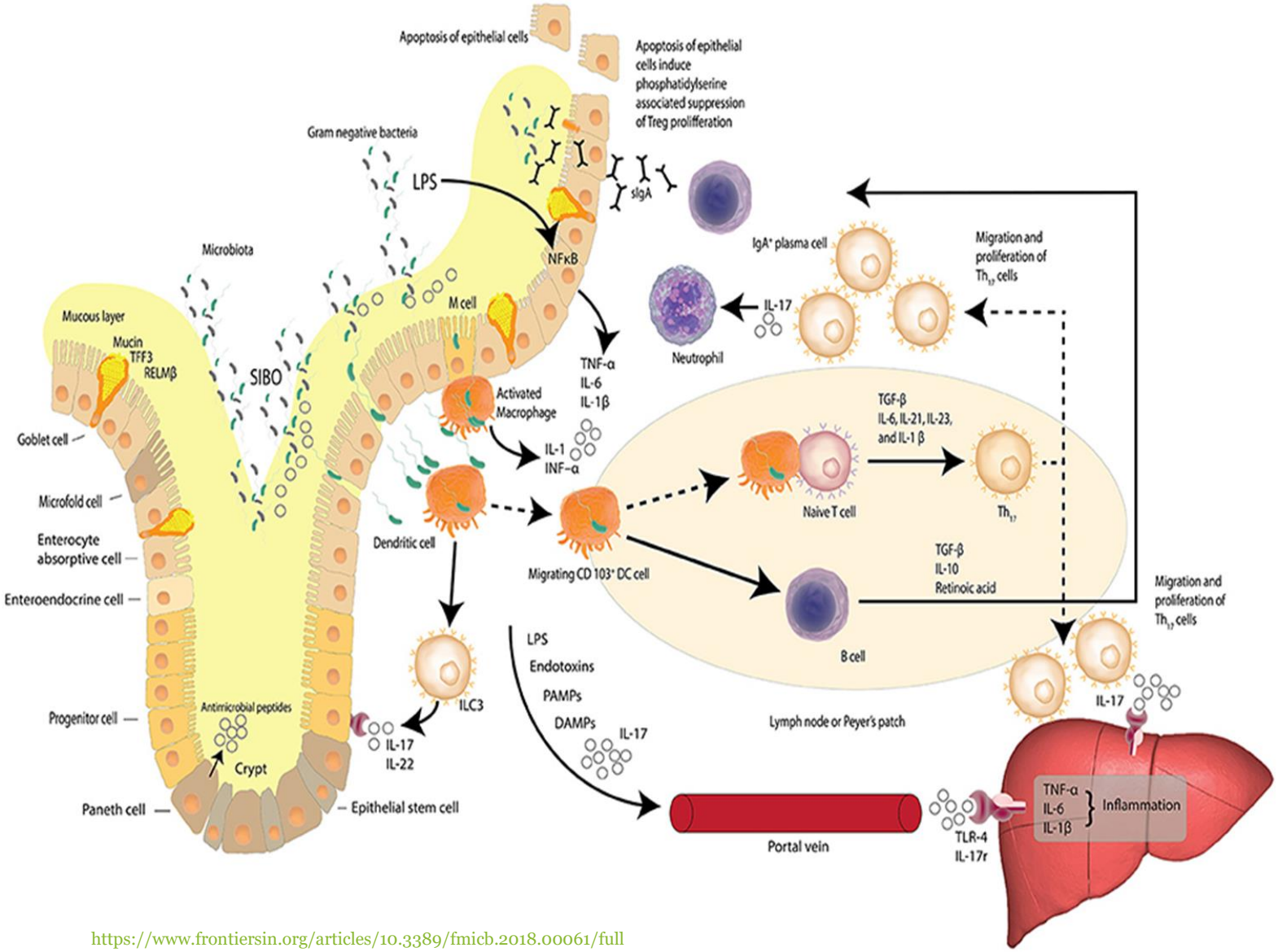
MCP-activated NK-cells, demonstrating functionality in inducing cancer cell death

BUILD Gut

- Eliminate food sensitivities and food allergies
- Eliminate pathogenic bacteria and yeast/mold
- Balance opportunistic bacteria, replenish probiotics
- Heal the gut lining; Glutamine, demulcent herbs, zinc
- Replace deficient micronutrients
- Digestive Enzymes
- Modified Citrus Pectin (MCP)
- Serum Derived Bovine Immunoglobulin (SBI)
- Eliminate gluten, dairy, and sugar
- Anti-inflammatory and phytonutrient-rich diet
- Intermittent fasting
- Adequate sleep
- Stress management

Restoring GI Integrity is KEY
(Saltzman, 2018)

- Immune distraction/dysregulation
- Systemic inflammation
- Endotoxin reabsorption
- Increased severity of Herxeimer
- Overburdens liver detox systems
- CNS Inflammation/Sx



https://www.frontiersin.org/articles/10.3389/fmicb.2018.00061/full

BREAK DOWN Biofilms

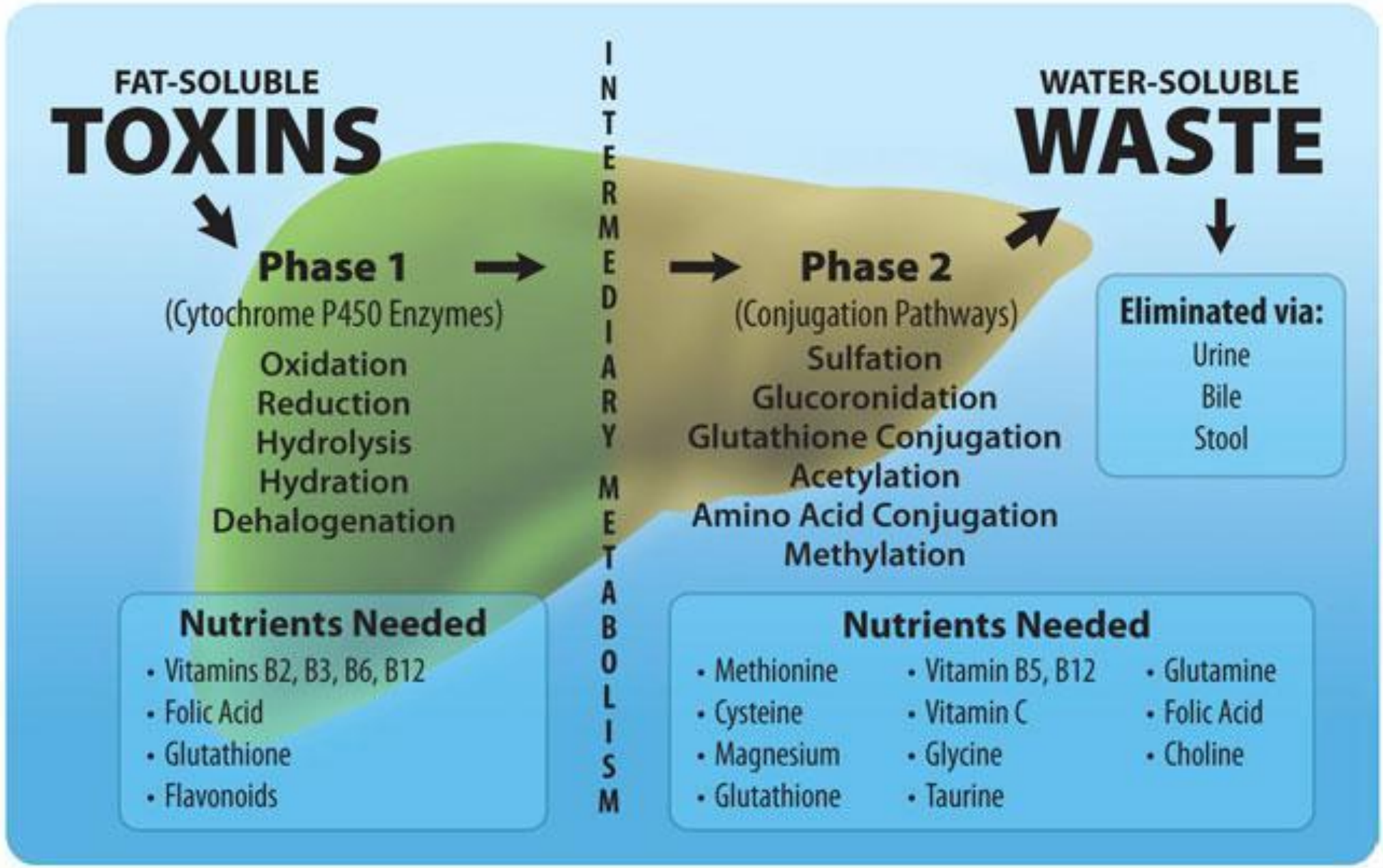
- **MCP** (Eliaz and Raz, 2019)
- **Serrapeptase & Nattokinase**: proteolytic enzymes (Tiwari, 2015)
- **Many botanicals:**
  - Berberine (Sun et al., 2015)
  - Curcumin (Rudrappa & Bais, 2008)
  - GSE (Heggers et al., 2002)
  - Oregano oil (Nostro et al., 2007)
  - Garlic (Allicin) (Naganawa et al., 1996)
  - Olive Leaf Extract (Sudjana et al., 2009)
  - Monolaurin (Preuss et al., 2005)

VII

BOLSTER Detoxification

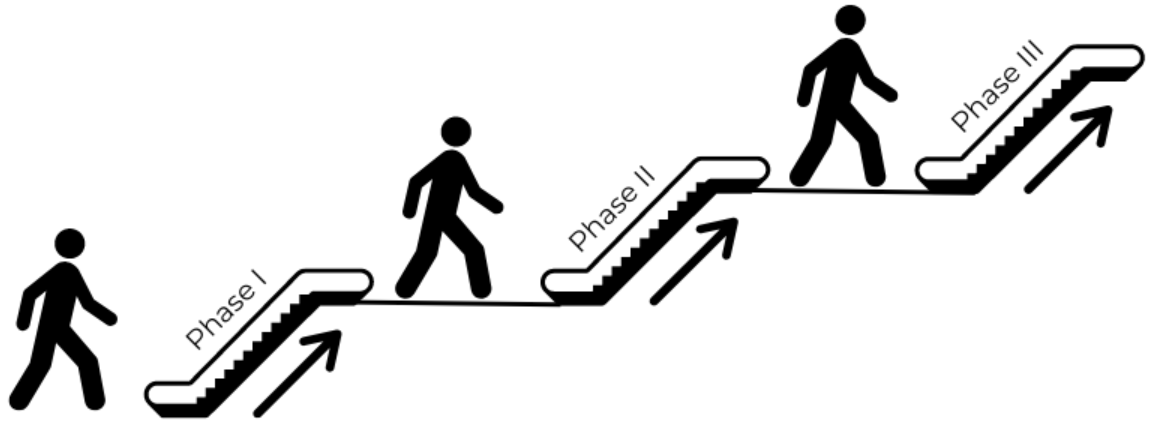
1. Fix tight junctions**: G3M, glutamine, butyrate, glutamine, tryptophan, zinc, EPA/DHA, A/D/C, polyphenols** (Rabbani et al., 2004; Suzuki, 2020).
2. Correct dysbiosis: **probiotics, berberine, GFSE** (Heggers et al., 2002; Zhang et al., 2021).
3. **Glycine (**Pérez-Torres et al., 2016).
1. GSH conjugation: **NAC, selenium, ALA, cruciferous veggies, curcumin, sulforaphane** (Minich and Brown, 2019).
2. Nrf2 induction: **sulforaphane** (Houghton et al., 2016).
3. Methylation: **Methyl folate, Methyl B12, B6, choline** (Łoboś et al., 2021).
4. Sulfation: **cysteine, methionine, molybdenum** (Jacob et al., 2003).
5. Acetylation: **B1, B5, Vit C** (Watson, 2021).
6. Glucuronidation**: cruciferous veggies, watercress, citrus, quercetin, curcumin, astaxanthin** (Novkovic, 2019).
7. Decrease B-glucuronidase: **calcium-d-glucarate, pre and probiotics, EGCG, Liver-milk thistle, artichoke, bupleurum root, vitamin C, magnesium** (Calicum D-GlucMaruti et al., 2010).
8. Binders of endotoxins: **chlorella, G3M, bentonite clay**, etc. (Watts, n.d.; Zhao et al., 2008).
9. Don’t forget routes of elimination and self care!

Detox Protocol – Stop Exposure

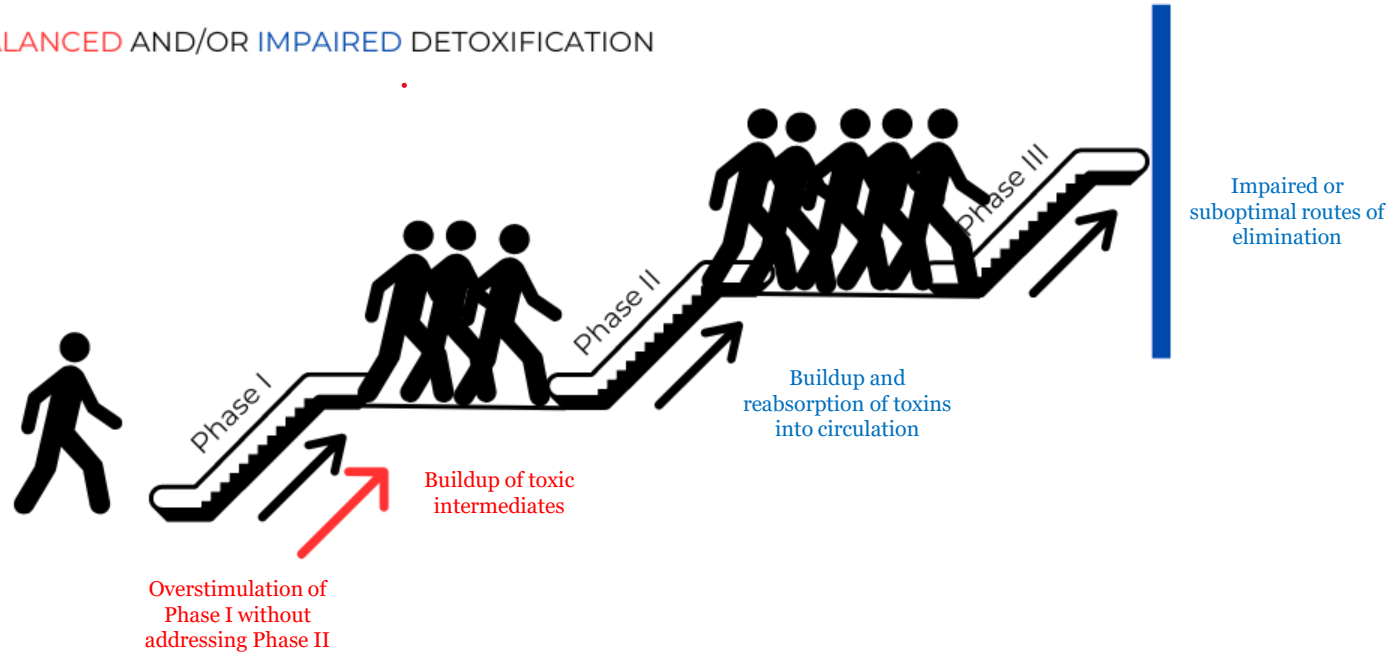


https://sa1s3optim.patientpop.com/assets/images/provider/photos/2476605.jpeg

NORMAL AND HEALTHY DETOXIFICATION

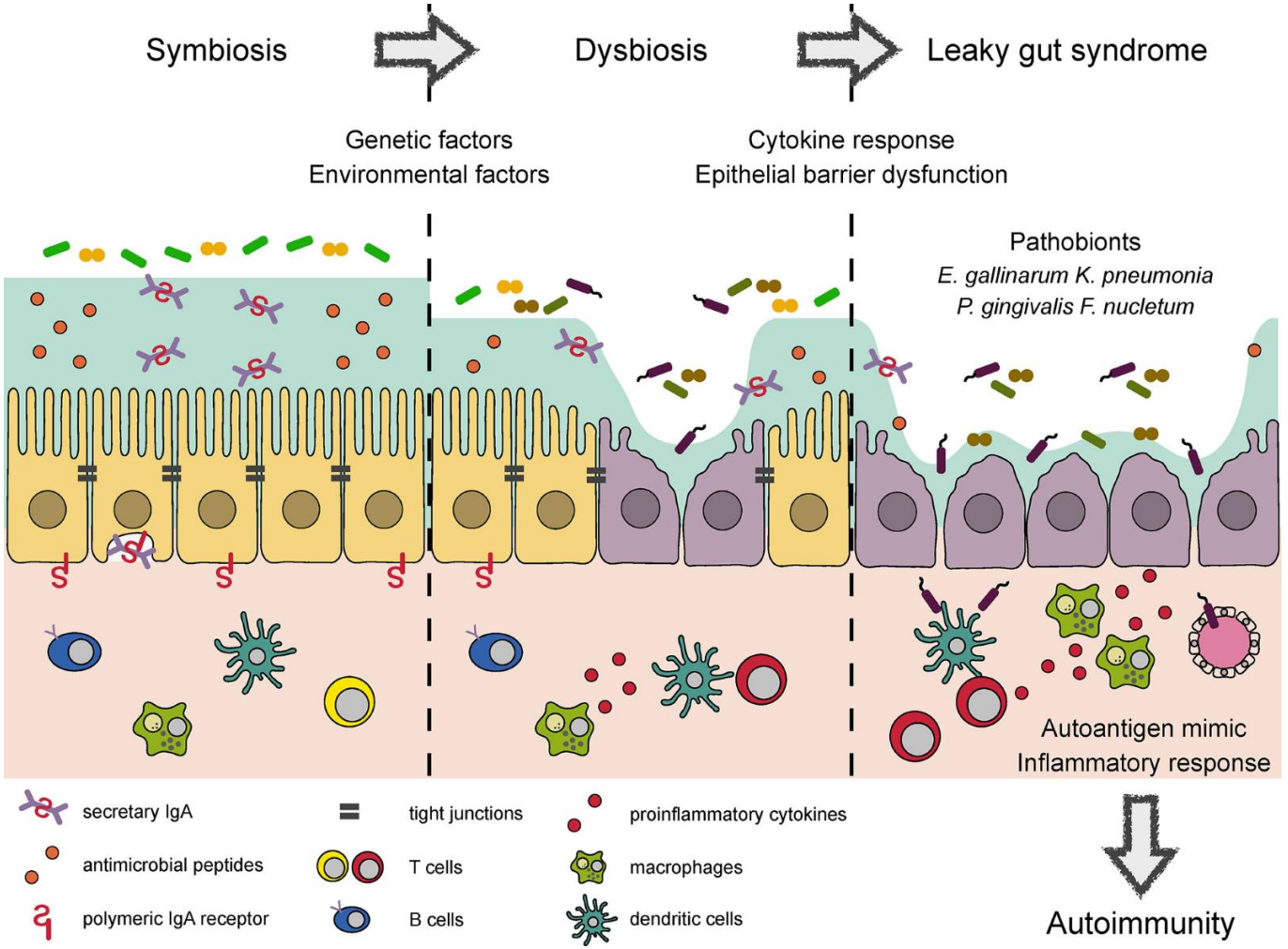


IMBALANCED AND/OR IMPAIRED DETOXIFICATION

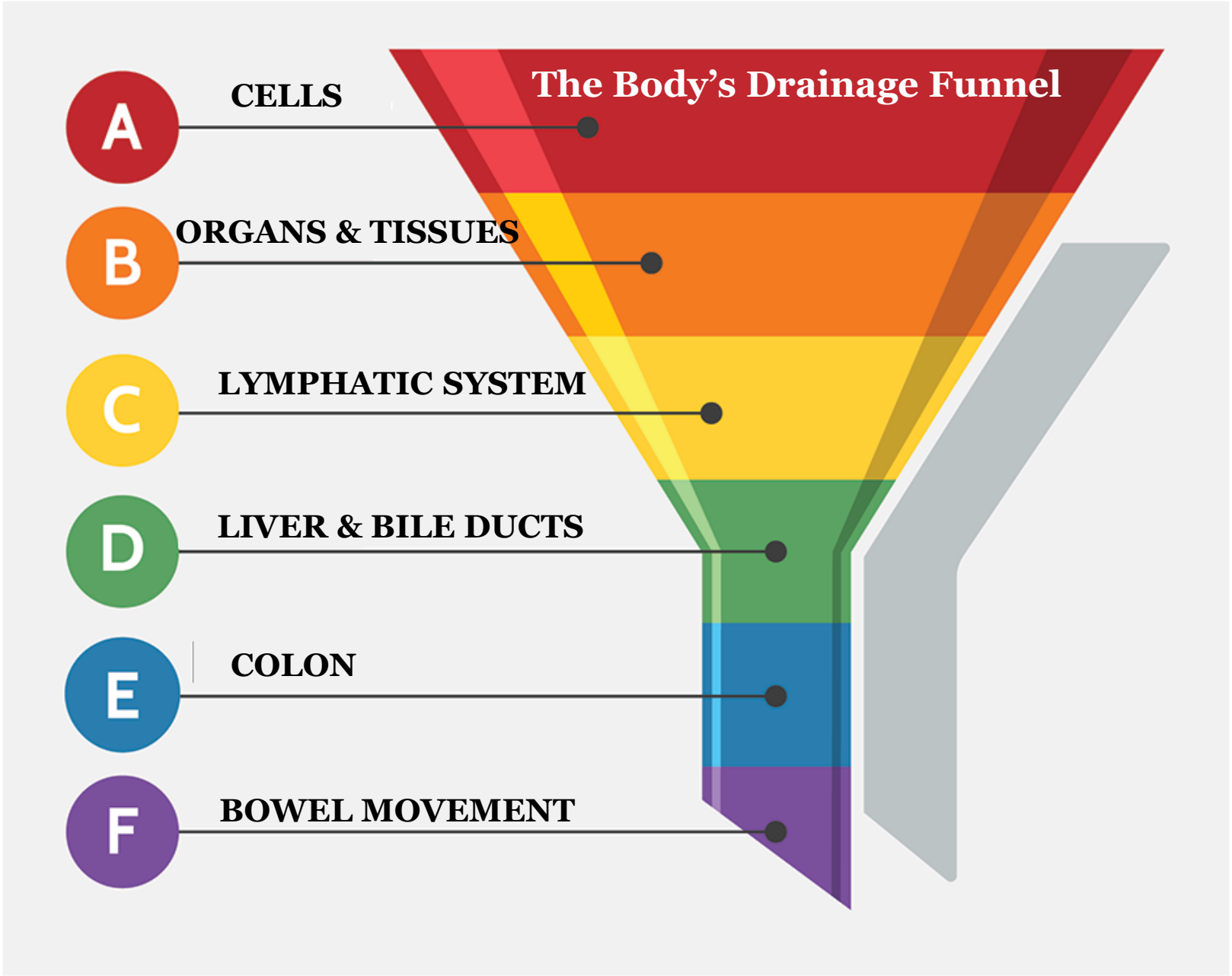


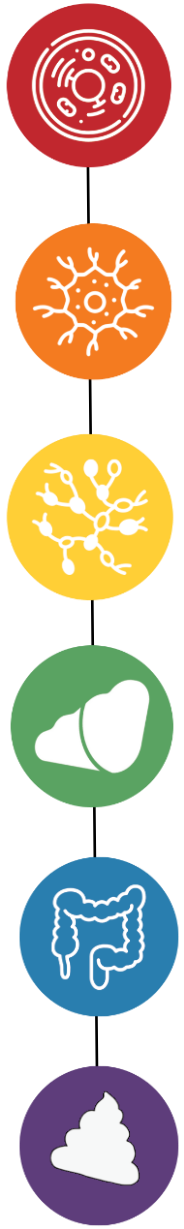
Cline, J.C. (2015). Nutritional aspects of detoxification in clinical practice. *Alternative therapies in health and medicine, 21 3*, 54-62 .

Role Of GI System In Detox



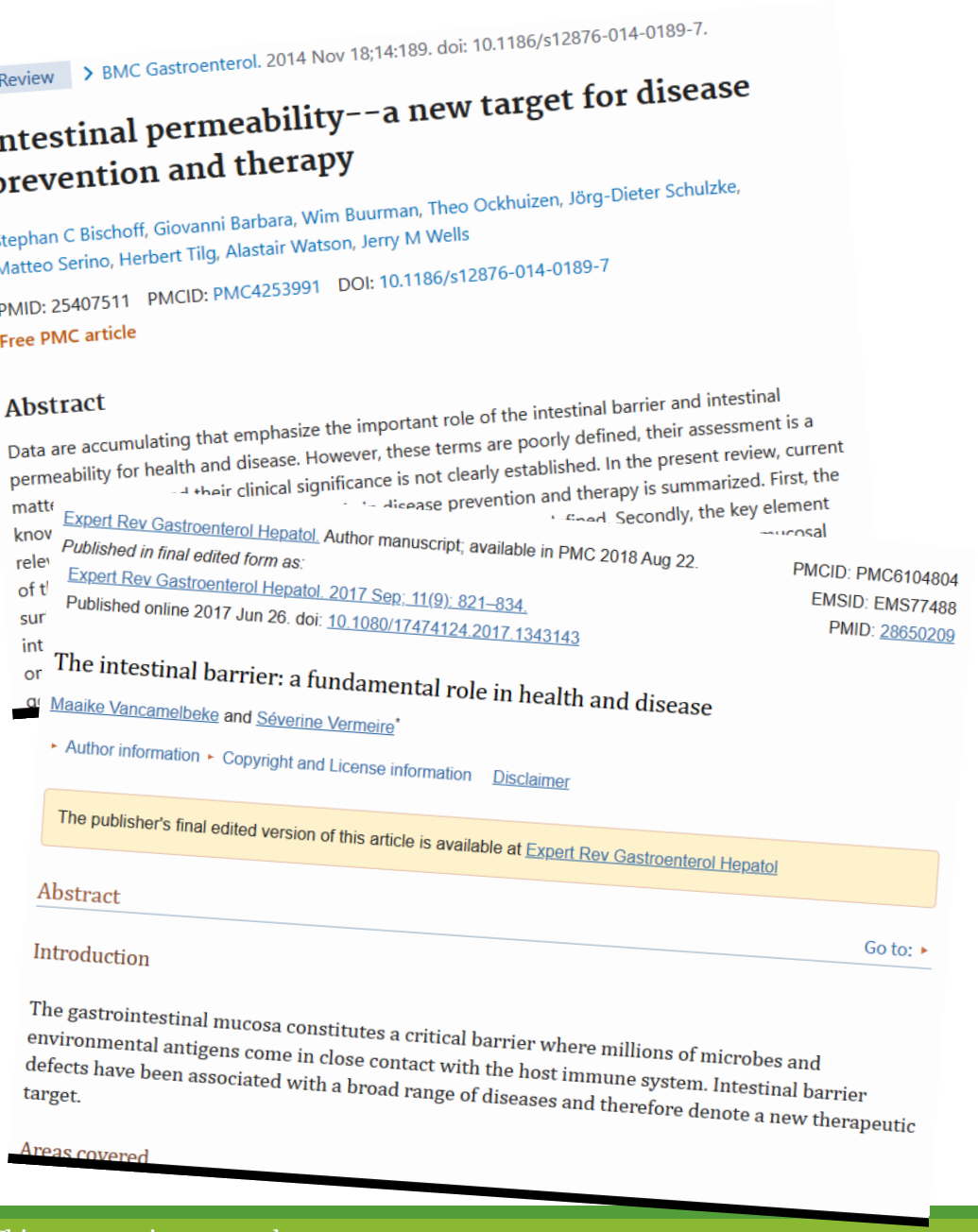
Kinashi, Yusuke, and Koji Hase. "Partners in Leaky Gut Syndrome: Intestinal Dysbiosis and Autoimmunity." *Frontiers in Immunology*, vol. 12, Apr. 2021, p. 673708. *DOI.org (Crossref)*, https://doi.org/10.3389/fimmu.2021.673708.





Detoxification Physiology

- Ramifications of increased permeability in toxicity
  - not properly digesting – leaking in undigested polypeptides, distracting and overreacting immune system, creating histamine and inflammation compounds, CNS inflammation
- Toxins in systemic circulation – lead to increased cytokines
  - Damage to organs, ROS, brain toxicity/CNS



Review > BMC Gastroenterol. 2014 Nov 18;14:189. doi: 10.1186/s12876-014-0189-7.

Intestinal permeability--a new target for disease prevention and therapy

Stephan C Bischoff, Giovanni Barbara, Wim Buurman, Theo Ockhuizen, Jörg-Dieter Schulzke, Matteo Serino, Herbert Tilg, Alastair Watson, Jerry M Wells

PMID: 25407511 PMCID: PMC4253991 DOI: 10.1186/s12876-014-0189-7

Free PMC article

Abstract

Data are accumulating that emphasize the important role of the intestinal barrier and intestinal permeability for health and disease. However, these terms are poorly defined, their assessment is a matte … their clinical significance is not clearly established. In the present review, current knov … disease prevention and therapy is summarized. First, the relev … fined. Secondly, the key element of t… …mucosal sur… int… or… q…

Expert Rev Gastroenterol Hepatol. Author manuscript; available in PMC 2018 Aug 22.

Published in final edited form as:

Expert Rev Gastroenterol Hepatol. 2017 Sep; 11(9): 821–834.

Published online 2017 Jun 26. doi: 10.1080/17474124.2017.1343143

PMCID: PMC6104804 EMSID: EMS77488 PMID: 28650209

The intestinal barrier: a fundamental role in health and disease

Maaike Vancamelbeke and Séverine Vermeire*

Author information ▸ Copyright and License information Disclaimer

The publisher's final edited version of this article is available at Expert Rev Gastroenterol Hepatol

Abstract

Introduction Go to: ▸

The gastrointestinal mucosa constitutes a critical barrier where millions of microbes and environmental antigens come in close contact with the host immune system. Intestinal barrier defects have been associated with a broad range of diseases and therefore denote a new therapeutic target.

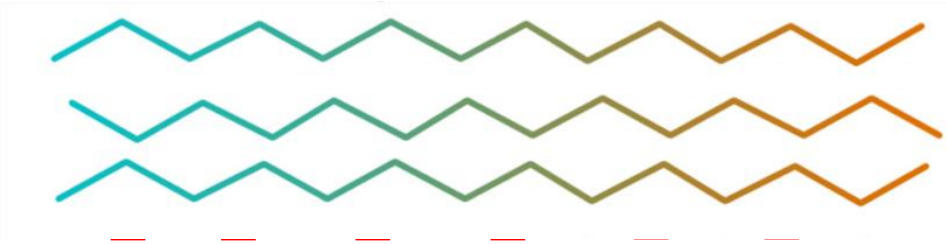
Areas covered

MCP Binding MOA with Heavy Metals

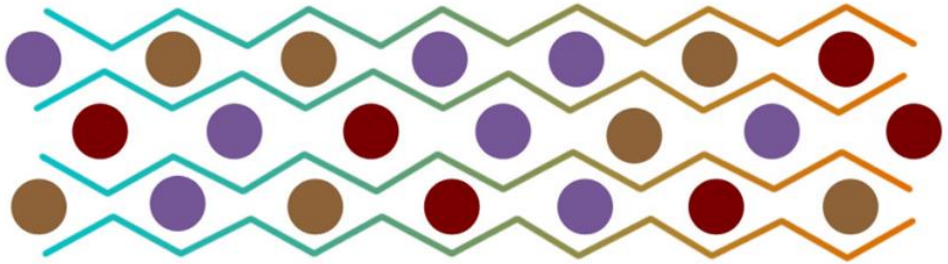
Heavy Metal Particles

- Mercury (Hg^{2+})
- Lead (Pb^{2+})
- Cadmium (Cd^{2+})

MCP Fiber Structure



Metals Become Trapped in Fiber



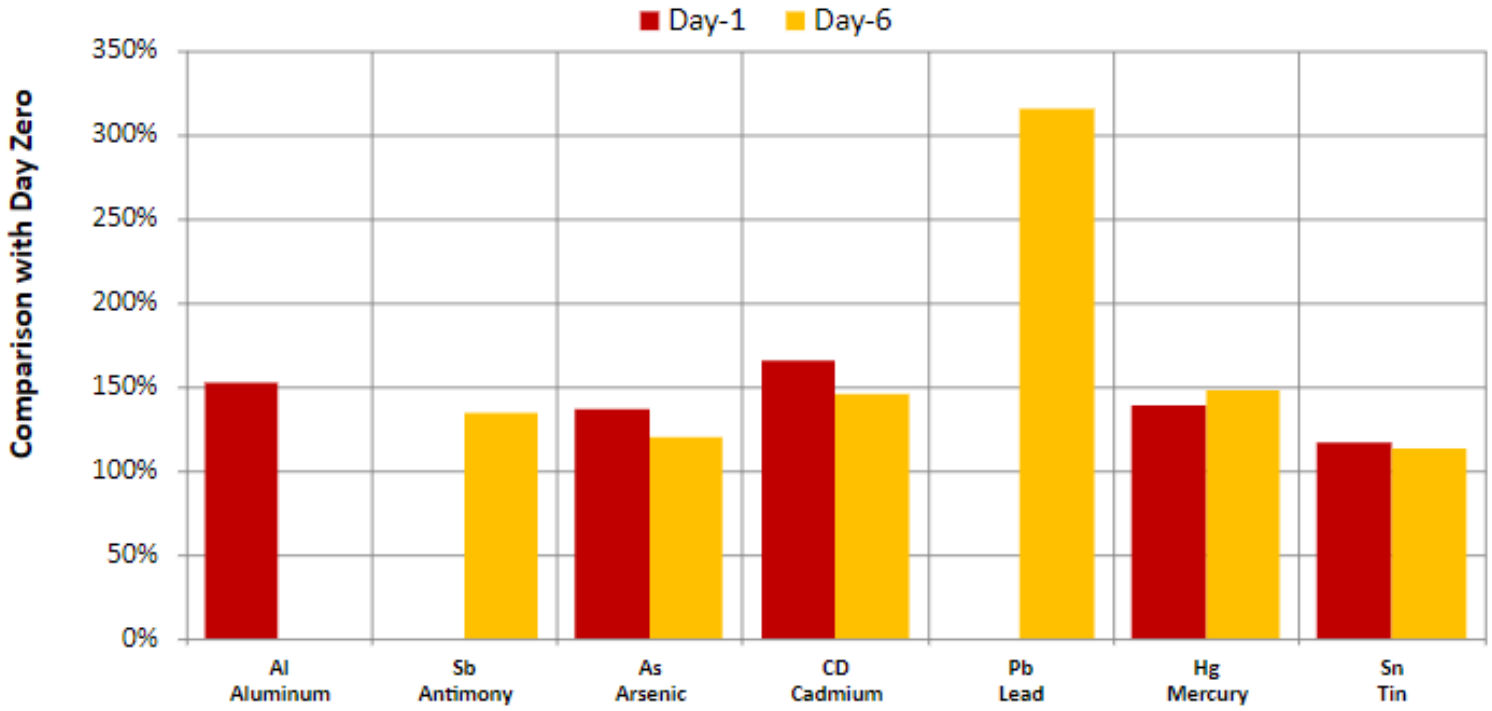
Essential minerals are not disturbed such as Ca^{2+} Cu^{2+} Mg^{2+}

Grant, Gregor T., Morris, Edwin R., Rees, David A., Smith, Peter J.C. and Thom, David(1973), Biological interactions between polysaccharides and divalent cations: The egg-box model, FEBS Letters, 32, doi: 10.1016/0014-5793(73)80770-7

Published Clinical Research: Effect of MCP on Urinary Excretion of Toxic Metals (Eliaz, 2006)

Methods:

- Healthy Subjects: (n=8)
- Oral MCP @ 15 grams QD x 5 days, and 20 grams on day 6
- 24 hr. urine samples collected day 0, 1, & 6



Results:

- **Dramatic decrease** in blood levels of lead (P=.0016; 161% ave. drop)
- **Dramatic increase** in 24 hr. urine levels (P=.0007: 132% ave. drop)

Detox Protocol:
Self Care Interventions

- Epsom salt baths
- Binders
- Hydration
- Infrared sauna
- Deep breathing
- Castor oil packs
- Dry skin brushing
- Cryo therapy or contrast therapy

BIND Endotoxins to Inhibit Jarish-Herxheimer Reaction

- Transient clinical phenomenon that occurs in patients infected by spirochetes who undergo antibiotic tx.
- Caused by the release of cytokines and lipoproteins enter the bloodstream that cause acute inflammatory changes (dilation of small BVs, dermal edema, perivascular and interstitial polymorphonuclear round cell, leucocytic infiltration).
- Fevers, chills, nausea, vomiting, headaches, tachycardia, hypotension, hyperventilation, flushing, myalgia, exacerbation of all symptoms due to heightened inflammation.

Treatment Goals: Products

1. Bind LPS: MCP, SBI, Chlorella (Eliaz et al., 2019; Jasion et al., 2015; Nakano et al., 2007; Petschow et al., 2015).
2. Detox: Tight junctions; Coordination of Ph1 and Ph2 liver (NAC), micronutrients for detox, elimination, self-care (sauna, epsom salt baths) (Hussain et al., 2018; Khoshbaten et al, 2010).
3. Alkalinization: Alkaseltzer Gold, chlorella, minerals, salts (Horowitz, 2013).
4. Anti-inflammatories: NAC, JKW, Chinese Skullcap (Buhner, 2005; Fujita, 2005; Kang, 2018; Sloan Kettering, 2023; Uraz et al., 2013).

Jarish-Herxheimer Reaction

Borrelia spp.

•Component of outer membrane of cell wall of Gr-ng bacteria (LPS)

•Passively released during cell death, mechanical damage, lysis, growth and division (not to be confused with exotoxins actively released into body from the bacteria)

•Can circulate long after bacterial infection has resolved. **Relies on detox for removal.**

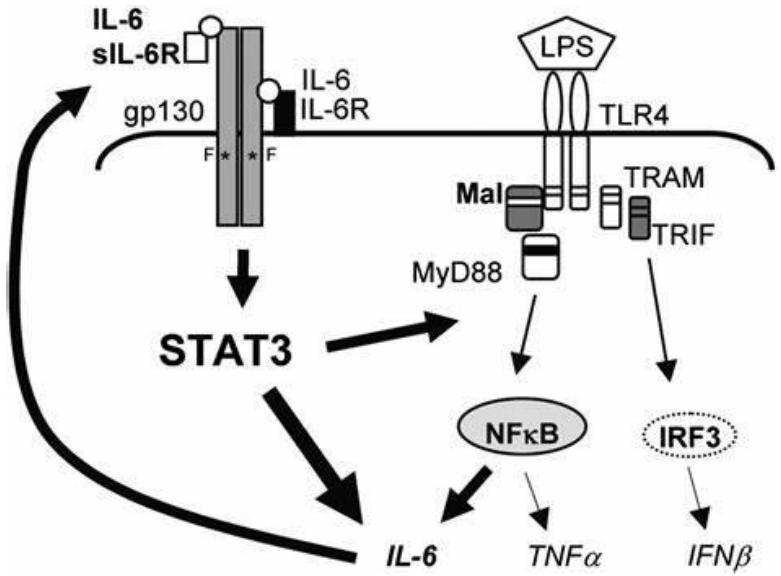
•Pyrogen even in picograms – in large amounts can cause shock and organ failure

Common sx:

•Diarrhea

•In the bloodstream (endotoxemia) can cause hypotension, reduced O2, respiratory failure, severe can lead to organ damage and death

Biochemistry of Herx



- Innate immune response – mediated by Toll-like Receptor 4 (TLR4) in complex with MD2
- TLR4 stimulated pro-inflammatory cytokines (IL1, IL 6, IL 8, TNF a, Platelet activating factor then prostaglandins and leukotrienes) and NO from macrophages and endothelial cells
- Stimulate B cell differentiation proliferation, IgG and IgM secretion
- Activates complement and coagulation cascades – inflammation, vasodilation, chemotaxis of neutrophils, coagulation, bleeding and shock

Claire J. Greenhill, Stefan Rose-John, Rami Lissilaa, Walter Ferlin, Matthias Ernst, Paul J. Hertzog, Ashley Mansell, Brendan J. Jenkins; IL-6 *Trans*-Signaling Modulates TLR4-Dependent Inflammatory Responses via STAT3. *J Immunol* 15 January 2011; 186 (2): 1199–1208. https://doi.org/10.4049/jimmunol.1002971

Clinical Presentations

- Oftentimes, we see that the quicker killing, the higher the toxic load and the more severe the reaction
- Fluctuation in body temp (38-41 C) with flu like sx and sweating, symptom flare, physiological changes
- Syphilis usually worst 24 hours then clears within days. Lyme 48-72 hours and can last for weeks, more with impaired detox and increased permeability.
- Usually unreported because symptoms of herx are that of the infection itself….
- According to JB – " for patients with CLD or late stage LD, the worst is around 4 weeks and is similar to serum sickness (leucopenia and increased liver enzymes)

Dhakal A, Sbar E. Jarisch-Herxheimer Reaction. [Updated 2023 Apr 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557820/

Herxheimer Reaction in Normal and Healthy Detoxification

	Jarisch-Herxheimer	Mild allergy/Intolerance	Anaphylaxis
Onset	24-72 hours after 1st dose of antibiotic	Minutes to days after starting medication	Minutes to hours after starting medication
Symptoms	Fever Chills Rigors Low blood pressure Headache Body pain Rapid heart rate Hyperventilation Rashes reappear Shock (rarely)	Mouth tingling Itchy throat/ears Stomach upset Nausea Diarrhea Constipation Body aches Sleep disturbance Ringing in the ears Wheezing	Swollen face Rapid heart rate Chest tightness Weak pulse Low blood pressure Airway restriction Rash, hives, blisters Nausea or vomiting Shock Fatal if not treated
Treatment	Anti-inflammatories, fluids, Detox	Anti-histamines, may need to stop medication if symptoms persist	Requires emergency treatment: Epinephrine, IV Benadryl, steroids.
Resolution	Days to weeks, may reoccur every 4 weeks	Several hours to few days	Several days to a week
Prevention	JH is a normal part of treating Lyme but should be closely monitored by a doctor who is trained in managing these cases	Avoid allergens/triggers	Avoid known allergens

LYME SCI: The dreaded Jarisch-Herxheimer reaction | BayAreaCannabis. Accessed 6/30/2023

Managing Herx – Acute Protocol

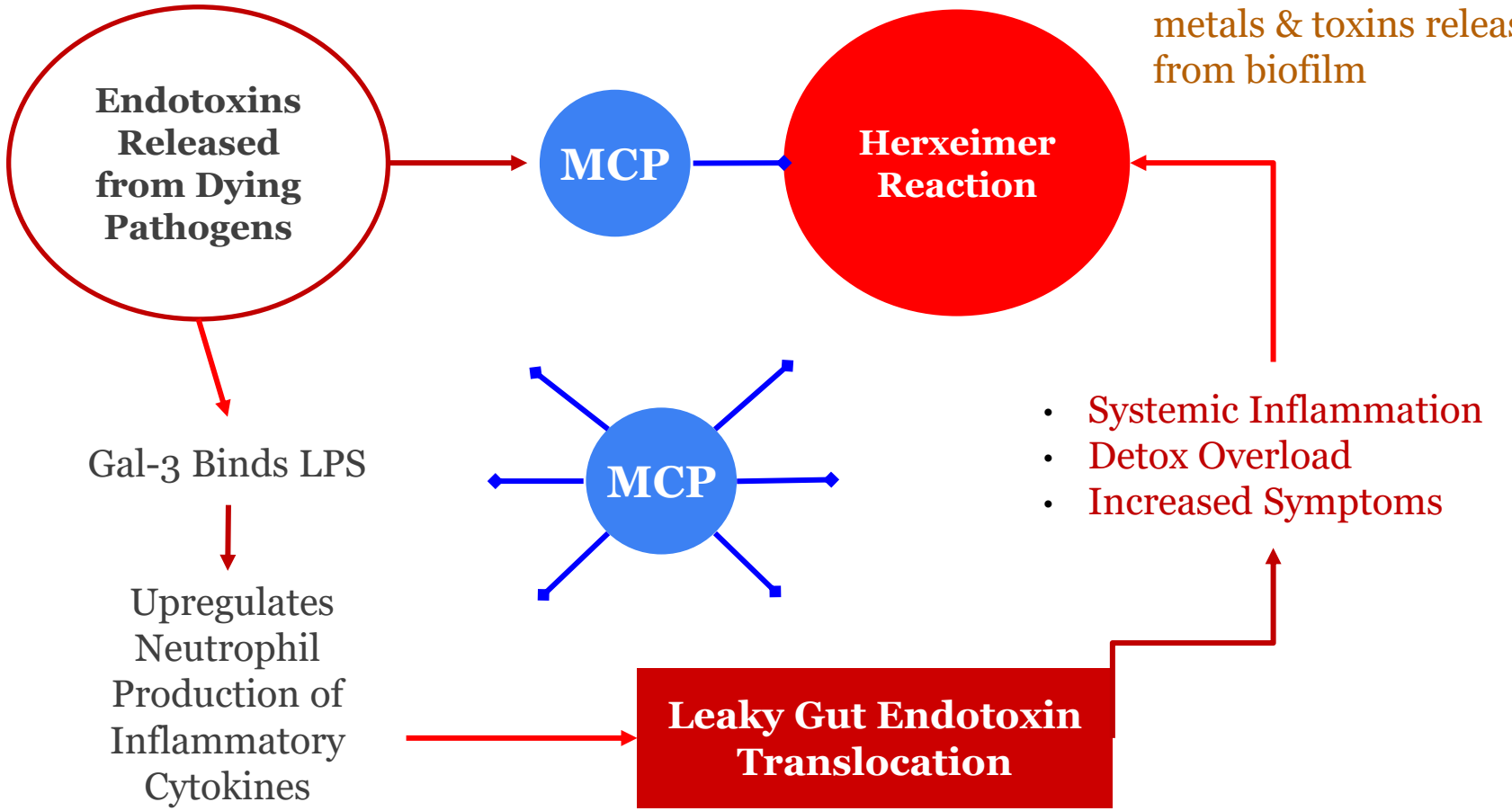
- **Binders**
  - Herbal formula (containing smilax glabra, cleavers, molybdenum)
  - MCP (Eliaz et al., 2019)
  - Chlorella (Nakano et al., 2007)
  - Bentonite clay, zeolite clay, activated charcoal (Schaumberger et al., 2014; Watts n.d.)
- **DETOX** – elimination, p1/p2 liver detox, self care
- **Stop the cytokine cascade**, specifically TNFa, IL6, IL8
- **Replenish minerals** to support biochemical reactions & minerals are alkalizing
- **Increase the body's protection against free radical damage** from resulting increase in endotoxins and inflammation
- **Horowitz' Protocol:** alkalize to combat acidic environment Lyme disease has created & improve methylation (Horowitz, 2013).
  - 1500mg of liposomal glutathione
  - Juice of 1 lemon
  - 2 Alka-Seltzer Gold tablets
  - 8 ounces of water

Horowitz, MD, Dr. Richard. "Lyme and Pain." *Why Can't I Get Better? Solving The Mystery of Lyme & Chronic Disease*. New York: St. Martin's, 2013. 430-31. Print.

As a Gal-3 & Toxin Binder: MCP Reduces Herxheimer Reactions

(Fermino, 2011)

MCP binds to Gal-3 to inhibit immune over-reactivity and inflammatory cytokine cascades



Fermino ML, Polli CD, Toledo KA, Liu FT, Hsu DK, Roque-Barreira MC, Pereira-da-Silva G, Bernardes ES, Halbwachs-Mecarelli L. LPS-induced galectin-3 oligomerization results in enhancement of neutrophil activation. PLoS One. 2011;6(10):e26004.

BLAST the Bugs: *Borrelia spp.*

- ***Artemesia spp* / Sweet Annie** (Feng, 2020)
- ***Andrographis paniculata*** (Feng, 2020)
- **Teasel** (Goc, 2016)
- ***Houttuynia cordata*** (Hayashi, 1995)
- **Garlic** (Kolb, 2020)
- **Olive leaf extract** (Borjan, 2020)
- ***Uncaria tomentosa* / Cat's claw** (Weiss, 2018)
- ***Scutellaria baicalensis* / Chinese Skullcap** (Feng, 2020)
- ***Juglans nigra* / Black walnut** (Feng, 2020)
- **Grapefruit Seed Extract** – Cyst and Round Bodies (Brorson, 2007)
- ***Cryptolepis sanguinolenta*** (Feng, 2020)
- ***Polygonum cuspidatum*** (Feng, 2020)

In vitro and *in vivo* growth inhibitory activitie
cryptolepine hydrate against several *Babesi*
Theileria equi

Gaber El-Saber Batiha, Amany Magdy Beshbishy, Luay M. Alkazmi, Eman H. Nadwa
Naoaki Yokoyama, Iku

Publishe

Borelis Pro phytomedicine for the complex treatment of Lyme borreliosis in children

y Against Stationary

Herb–Drug Interaction Potential of Anti-Borreliae Effective Extracts from *Uncaria tomentosa* (Samento) and *Otoba parvifolia* (Banderol) Assessed In Vitro

Johanna Weiss

▸ Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

h novel

Abstra
Author
Introdu
Results
Discus
Materia
Suppor
Acknov
Refere
Reade
Figures

In Vi
the D

by Aks
Lyme I
Univers

Abstrac

A tick-b
burgdor
treatmer
often oc
B. burg
spiroche
need to
burgdor
(one of
effectiven
round boc
viability s
had very
suggestin

Abstract

Samento (extract from *U*
demonstrated to have an
morphological forms of *E*
pharmacological safety o
possible characteristics a
cytochrome P450 enzym
transporters by use of flu
and activation of pregnan
assays. Organic anion tra
(IC_{50} = 0.65 ± 0.29%) we
was inhibited about 40%
expression of *CYP2J2*, *UG*

Botanical Medicines Cryptolepis sanguinolenta, Artemisia annua, Scutell
baicalensis, Polygonum cuspidatum, and Alchornea cordifolia Demonstra
Activity Against Babesia duncani

Yumin Zhang,[1] Hector Alvarez-Manzo,[1] Jacob Leone,[2] Sunjya Schweig,[3] and Ying Zhang[4,*]

▸ Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

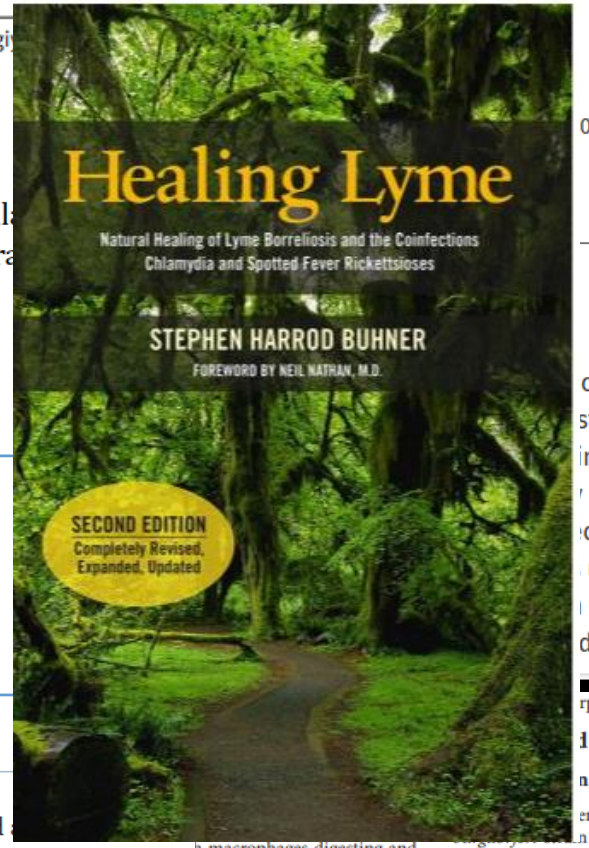
Associated Data

▸ Supplementary Materials

▸ Data Availability Statement

Abstract

Human babesiosis is a CDC reportable disease in the United States and is recognized
health risk in multiple parts of the world. The current treatment for human babesiosis is suboptimal
due to treatment failures and unwanted side effects. Although *Babesia duncani* was first described



0000069

Metrics

cat scratch
stemic
infections with
due in part to
d for treating
unknown. In
this study, we
d an herbal

ibiotics, which is why other bacteria *in vitro*.
was examined in the hopes
compound were utilized in
loreover, the MIC for both formulas. Additionally, the
ich as these are required in
posites might offer new Here, two commercially nd LSF Broad-Spectrum fficiency in eliminating
rphic forms of *B. burgdorferi in vitro*.

l methods

n, culturing conditions and test compounds

ents were conducted with infectious, fluorescent *B.* n GCB726 with GFP, which was graciously provided by Georges Chaconas, University of Calgary, Canada [11]. Barbour-Stoenner-Kelly medium (BSK II) [12], without gelatin and supplemented with 6% heat inactivated rabbit serum (Sigma-Aldrich, St. Louis, USA) was used in the culturing of cells at +37 °C. Low-passage number cells

effective for
continue to
anecdotal re
persisting sy
unclear whe
antimicrobia
study, we inv

10-2
repo
degr
direc
inves
natu
natural product ex
burgdorferi culture
botanicals include
(Japanese knotwee
incanus, and *Scute*

34 essential oils against *B. bu*
found that not all essential oi
top five essential oils (oregan
concentration of 0.25% showi
persister drug daptomycin. In

derived compou

Methods and F

We tested the ef
morphological f
latent rounded f

h macrophages digesting and
s [4]. Hence, examinations of
us forms.

Borrelia infected patients report signs and symptoms ranging from

activity
current treatments for Lyme disease, and offering new options to already existing therapeutic regiments.

Keywords: biofilm, *Borrelia sp.*, cysts, micronutrients, phytochemicals, spirochetes

Recent Study on *Borrelia burgdorferi*

ORIGINAL RESEARCH article

Front. Med., 21 February 2020 | https://doi.org/10.3389/fmed.2020.00006

Evaluation of Natural and Botanical Medicines for Activity Against Growing and Non-growing Forms of *B. burgdorferi*

Jie Feng, Jacob Leone, Sunjya Schweig, Ying Zhang

"This study provides the first convincing evidence that some of the herbs used by patients, such as **Cryptolepis, black walnut, sweet wormwood, cat's claw, and Japanese knotweed**, have potent activity against Lyme disease bacteria, especially the dormant persister forms, which are not killed by the current Lyme antibiotics,"

says study co-author Prof. Ying Zhang

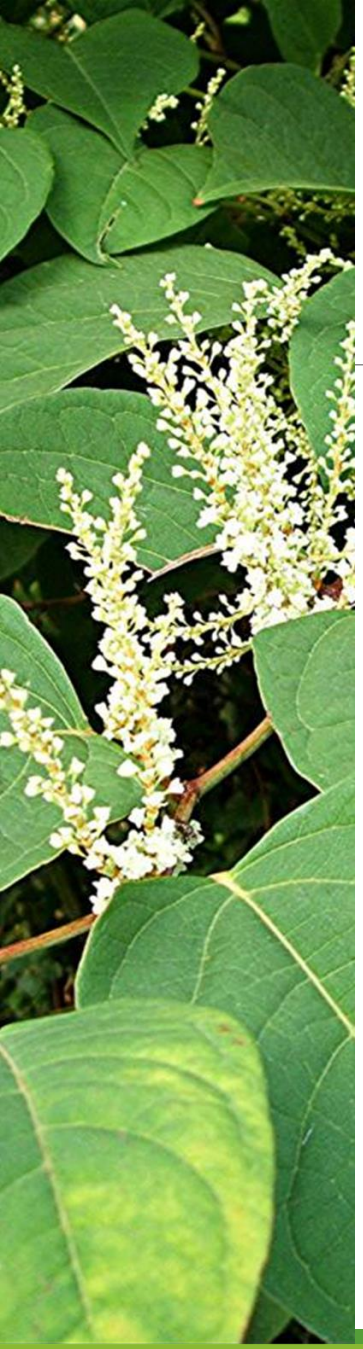
My 7 Most Used Antimicrobials for *Borrelia spp.*

1. Japanese knotweed (*Polygonum Cuspidatum*)
2. Cats claw (*Uncaria tomentosa*)
3. Chinese Skullcap (*Scutellaria baicalensis*)
4. Sweet annie (*Artemisia annua*)
5. Cryptolepis (*Cryptolepis sanguinolenta*)
6. Houttuynia (*Houttuynia cordata*)
7. Black walnut (*Juglans nigra*)

Polygonum Cuspidatum
Japanese knotweed

Anti-inflammatory

- Inhibition of the cellular immune system and inhibition of the formation of pro-inflammatory cytokines by emodin, resveratrol, citreorosein etc. (Buhner, 2005; Patocka, 2017; Guo, 2018)
- Inhibition of MMP-1, MMP -3 and MMP-9 expression by resveratrol and rhein (Buhner, 2005; Kang, 2018)
- Suppression of serotonin-induced swelling (Zhang, 2013)
- Inhibition of CRP and rheumatoid factor positive responses (Zhang, 2013)



Polygonum Cuspidatum Japanese knotweed

Immunomodulant/Immunostimulant

- Normalizes immune response, ex. response to antigen signal, proliferative capacity, IL-2 production, lymphocyte antibody production and regulatory T cell expansion, in inflammatory and autoimmune conditions (Patocka, 2017; Espinoza, 2017)

- Enhances phagocytosis of macrophage and natural killer cell activities in leukemic mice (Chueh, 2015)

Neuroprotective

- Active on CNS due to ability to cross blood/brain barrier (Buhner, 2005)
- Protects against hypoxic-ischemic brain injury via upregulation of brain-derived neurotrophic factor (BDN) and inhibition of cell adhesion molecules by polydatin (Patocka, 2017; Zhang, 2013)

- Protects against beta-amyloid-induced neurotoxicity and ischemic injury by emodin (Zhang, 2013)

Contraindications: pregnancy (Buhner, 2015)

Side Effects: abdominal pain, diarrhea, dry mouth, nausea, vomiting (Buhner, 2015)

Herb/Drug Interactions: blood-thinners (Buhner, 2015)

Uncaria tomentosa
Cat's Claw

Anti-inflammatory

- Inhibition of NF-kappaB (Batiha, 2020)

Antioxidant

- Inhibition of lipopolysaccharide-induced inducible nitric oxide synthase (iNOS) gene expression, nitrite formation, cell death and the activation of NF-kappaB (Batiha, 2020; Sandoval-Chacón, 1998)

Anti Spirochetal

- Effective against all morphological forms of *Borrelia burgdorferi*- spirochetes, round bodies, and biofilm-like colonies (Weiss, 2018)

Uncaria tomentosa
Cat's Claw

Cardioprotective

- Antiarrhythmic and negative chronotropic activity via direct effects on the action potential of cardiac muscle through inhibition of multiple ion channels by hirsutine and dihydrocorynantheine (Masumiya, 1999)
- Hypotensive effect on both systolic and diastolic blood pressures by gambirine (Mok, 1992)

Immunostimulant

- Stimulates proliferation of myeloid progenitors and normal resting B and T cell lymphocytes (Farias, 2011)
- Enhances IL-1 and IL-6 in lipopolysaccharide-stimulated macrophages (Lemaire, 1999)
- Increases natural killer cell CD57+ expression (Buhner, 2005)

Contraindications: immunosuppressive therapy, pregnancy or woman attempting to get pregnant (Buhner, 2005; Kuhn, 2008)
Side effects: constipation, diarrhea, digestive upset, mild lymphocytosis (Kuhn, 2008)
Herb/Drug Interactions: antihypertensives, blood thinners, immunosuppressants (Kuhn, 2008)

Scutellaria baicalensis Chinese skullcap

Antibacterial/Anti Spirochetal

- Via destruction of bacterial nucleic acid formation, altering bacterial energy metabolism and inhibiting the formation of bacterial biofilms via baicalin and baicalein (Sloan Kettering, 2023)
- *In vitro* activity against log phase spirochetes, latent round bodies, and biofilm formations of *B. burgdorferi* and *B. garinii* via baicalein (Zhao, 2016; Liao, 2021)
- Baicalein also exhibits synergistic activity when paired with various antibiotics (Zhao, 2016; Yin, 2021; Feng, 2020; Goc, 2015)

Anti-inflammatory

- Inhibition of the production of inflammatory factors TNF-α, IL-1β, Interleukin-6 (IL-6), Interleukin-17 (IL-17), matrix metalloprotein-9 (MMP-9), and regulation of NF-κB signaling pathway via baicalin (Sloan Kettering, 2023; Fujita, 2005)
- Inhibition of interleukin-8 release and COX-2 synthesis and upregulation of the formation of heat shock protein 70 via baicalein (Sloan Kettering, 2023; Cai, 2016)

Neuroprotective

- Baicalin exhibits a variety of beneficial effects in the central nervous system (CNS) by promoting neural differentiation and inhibiting neuronal apoptosis (Wang, 2019; Dinda, 2017)
- In rat model of collagenase-induced intracerebral hemorrhage baicalin administration reduced brain edema, inhibited NF-κB activation, suppressed MMP-9 expression and reduced the production of IL-1β and IL-6, as well as BBB permeability (Wang, 2019; Tian, 2015)

Artemisia annua
Sweet Annie

Antibabesial/Antiplasmodial

- Inhibition of *in vitro* or *in vivo* growth of *B. gibsoni*, *B. equi*, *B. bigemina*, *B. bovis*, and *B. microti* by artemisinin and its derivatives most likely due to its ability to generate free radicals which can damage pathogen DNA and proteins (Zhang, 2021)
- Artemisinin based compounds can reduce malarial parasitemia more rapidly than other known antimalarial drugs and are effective against all stages of *Plasmodium* spp (Zhang, 2021)

****Effective in 95-100% of mice infected with malaria** (Septembre-Malaterre, 2020)

Antibacterial/Anti Spirochetal

- Inhibition of a number of both gram positive and gram negative bacteria (Septembre-Malaterre, 2020; Kim, 2015)
- Directly effective against the stationary phase of *B. burgdorferi* and more effective than the control antibiotics cefuroxime and doxycycline. (Buhner, 2005; Kim, 2015)
- Artemisia ketone is the oil component that has the greatest antimicrobial activity (Septembre-Malaterre, 2020)

Artemisia annua Sweet Annie

Anti-inflammatory

- Suppression of pro-inflammatory cytokine production, including IL-1β, IL-6, IL-10, and TNF-α (Kim, 2015)
- Suppression of NF-κB, toll-like receptors (TLRs), signal transducer and activator of transcription (STAT) activity PI3K/protein kinase B (AKT) activity (Xia, 2020)

Antioxidant

- Mostly by hydrogen atom transfer rather than single-electron transfer (Septembre-Malaterre, 2020)
- Chrysoprenol D, a flavonoid, has been identified as the main constituent contributing to antioxidant activity (Septembre-Malaterre, 2020; Messaili, 2020)
- Diet containing the extract of *Artemisia annua* reduced serum levels of biomarkers for lipid peroxidation and DNA damage (Septembre-Malaterre, 2020; Kim, 2014)

Contraindications: pregnant and breastfeeding women (Kuhn, 2008; Buhner, 2005)

Side Effects: gastric upset, nausea, diarrhea, vomiting, dizziness and headache (Kuhn, 2008; Buhner, 2005)

Herb/Drug Interactions: azole antifungal agents and calcium channel blockers can negatively affect artemisinin absorption (Kuhn, 2008)

Cryptolepis sanguinolenta

Antibacterial/Anti Spirochetal

- DNA intercalation and topoisomerase II inhibition (Tempesta, 2010; Paulo, 1994; Cimanga, 1991)
- Activity against both Gram-positive and Gram-negative bacteria via cryptolepine (Tempesta, 2010; Paulo, 1994; Ansah, 2005)
- Directly effective against the stationary phase of *B. burgdorferi* and more effective than the control antibiotics cefuroxime and doxycycline (Feng, 2020)

Antimalarial/Antibabesial

- Inhibition of hemozoin polymerization (Tempesta, 2010; Onyeibor, 2005)
- Oral administration of water extract of *C. sanguinolenta* containing the cryptolepis alkaloids indicated efficacy comparable to chloroquine (Coronado, 2014)
- *B. duncani* treated with cryptolepine and quinine or *C. sanguinolenta* 90% ethanol extract could not regrow in subculture (Tempesta, 2010)

Anti-inflammatory

- Inhibition of nitric oxide production and DNA binding of NF-κB following inflammatory stimuli via cryptolepine (Tempesta, 2010; Zhang, 2021)

Contraindications: pregnant women and women of reproductive age who want to conceive (Tempesta, 2010)

Side Effects: generally well tolerated, few side effects have been documented in humans (Feng, 2020)

Houttuynia cordata

Antibacterial

- Myrcene, an essential oil, has an antimicrobial activity and moreover enhances the activity of antibiotics (National Parks, 2023)
- Profound inhibition of bacterial biofilm formation (Yang, 2009; Řebíčková, 2020)
- Houttuynin (decanoyl acetaldehyde), a β-dicarbonyl compound, is reported as a major anti-bacterial constituent (Sekita, 2016; Sekita, 2016)

Anti-inflammatory

- Downregulation of TNF-α and IL-6 and inhibition of NF-κB activation (Kumar, 2014; Duan, 2008)

Antioxidant

- Free radical scavenging activity of methanolic extract mainly due to catechin, procyanidin B (Sekita, 2016; Kim, 2007; Lee, 2013)

Juglans nigra Black walnut

Antibacterial/Anti Spirochetal

- *In vitro* testing exhibited bacteriostatic activity against log phase spirochetes of *B. burgdorferi* and *B. garinii* and bactericidal activity against *Borrelia* round bodies (wildflower.org, 2017; Paudela, 2013)
- Activity against Staphylococcus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Bacillus subtilis and Proteus vulgaris (Ho, 2018)
- Majority of antibacterial activity via juglone, Glansreginin A, azelaic acid, quercetin, and eriodictyol-7-*O*-glucoside (Feng, 2020; Goc, 2016)

Anti-inflammatory

- Via inhibition of proinflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-8, IL-10 and MCP-1 (Rathi, 2014)

Side effects: uncommon, nut allergies

Contraindications: Hashimotos

Lyme Disease *Sample* Herbal Protocol

,

- **MCP**: 1 tsp TID
- ***Withania somnifera***: ½ tsp TID
- ***Polygonum cuspidatum* root**: ¼ tsp TID
- ***Uncaria tomentosa***: ¼ tsp TID
- ***Cryptolepis sanguinolenta***: ½ tsp TID
- ***Scutellaria baicalensis***: ¼- ½ tsp TID
- ***Artemisia annua***: ¼ tsp TID
- ***Juglans nigra***: ¼ tsp TID
- **GFSE**: 600-1200 mg BID
- *Consider others depending on individual symptoms*

For Effective Resolution or Remission of Lyme, You Must Understand….

The Infection

Understand how the infectious organism thrives in the body

The Terrain

Understand how the patient's circumstances are making the body hospitable to infection

The Treatment

Understand the MOAs of the medications, herbs, and nutraceuticals available to you

…then you can create an intelligent, effective treatment plan!

Halting Initial Infection And Healing Babesia

Persistence of Babesia

- In the blood vessels of many organs (esp. spleen and liver), babesia sequesters many forms of itself: merozoites, gametocytes, ookinetes, sporozoites (Chauvin, 2009)

- Even after successful antibiotic therapy (blood smear is clear), the disease can recur, usually within 2 weeks to a month (Ho, 2021)
  - From these sequestered locations, new sporozoites are released that infect new RBCs and the cycle starts all over again

- New cycle:
  - offspring has resistance to pharmaceuticals as it has learned the mechanism that had previously killed them through pleomorphism, or altered genetic structure and body shape (Chauvin, 2009)
  - can be asymptomatic for a while and then turn relapsing

Babesiosis – Areas of Invasion

- Can cause anemia (high percent of RBC infected) or petechiae from infected capillaries (Woolley, 2017)
- Areas of highest levels of infection:
  - RBC (Lobo, 2012)
  - Endothelial cells that line blood vessels (Wright, 1989)
  - Spleen – ultimately clears infection (Djokic, 2018)
    - **Red sage and red root protective of the spleen (Xiping, 2009)**
  - Liver (Nassar, 2017)

Nitric Oxide (NO)

- Under normal circumstances, RBC releases NO when a parasite attaches to RBC
- NO surrounds the cell and upon release, forms a toxic gas cloud that lasts for seconds to kill many bacteria and parasites
- Babesia releases a compound very similar to arginase – the enzyme that down regulates the production of NO by RBC (by breaking down arginine)
- This takes away the main RBC defense of babesia infection (Aguilar-Delfin, 2003)

Increasing NO production:

- **L-arginine** (Boger, 2014)

Cyclin-dependent kinases (CDK)

Once merozoite gets inside the RBC, it replicates by:

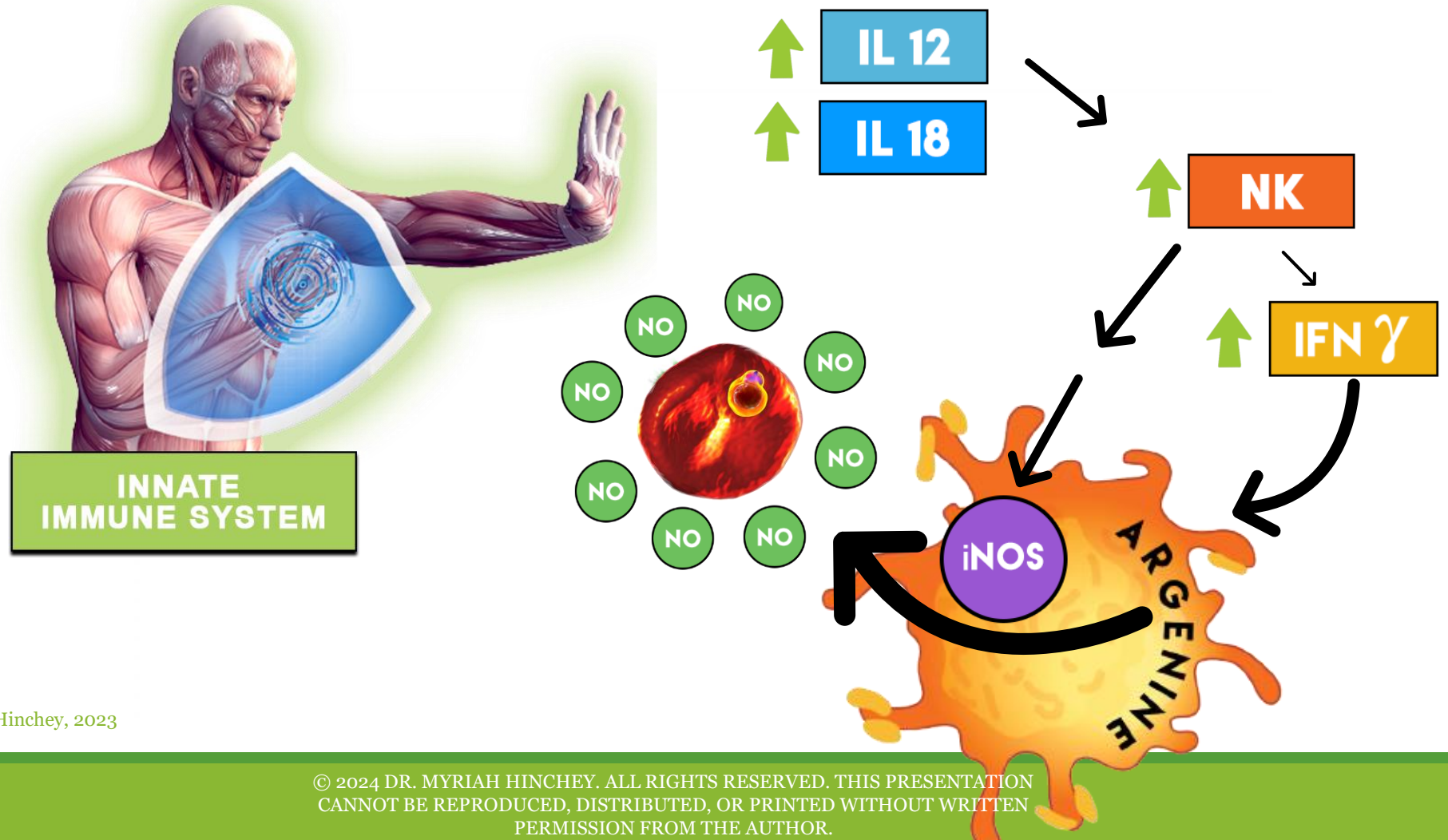
- creating a parasitophorous vacuole (PV) made from lipids
- PV is broken down in 10 mins, releasing the envacuoled merozoite into the interior of the RBC
- creates new nuclei divides via fission, 2-4 new babesia cells are created

Process is regulated by cyclin-dependent kinases (CDKs). Replication cannot occur without them.

CDK inhibitors:

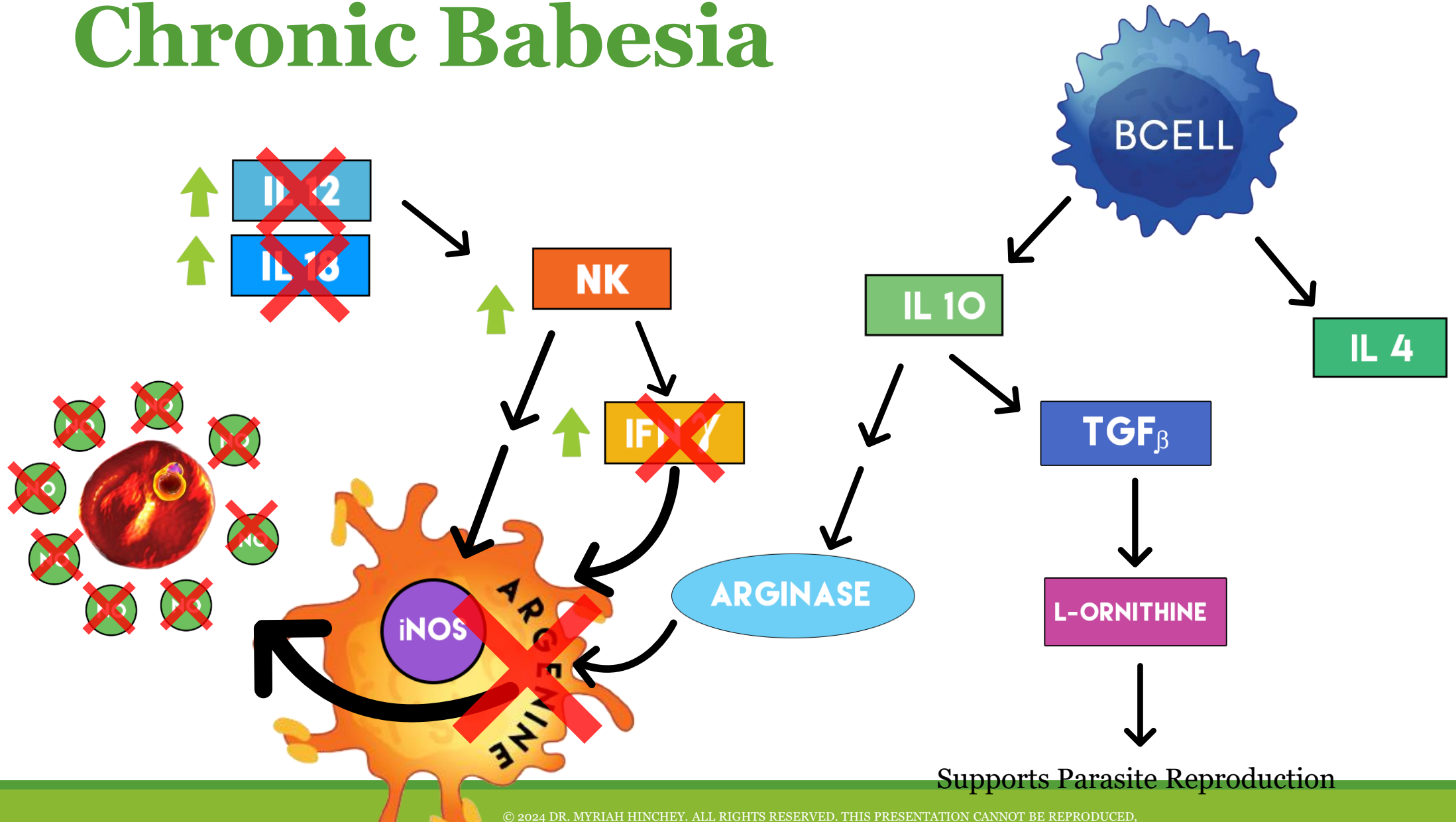
Licorice (Lee, 2013), ***Artemisinin/Sweet Annie*** (Gray, 2016), ***Chinese skullcap*** (Hsu, 2001), **Ginger** (Lin, 2012), ***Peganum harmala*** (Li, 2007), ***Eurycoma longifolia*** (Li, 2007), ***Magnolia officinalis*** (Lee, 2006), ***Dunaliella salina*** (Sheu, 2008)

Acute Babesia



Proprietary image created by Myriah Hinchey, 2023

Chronic Babesia



SUMMARY: Successful Resolution of Babesia

1. Spleen's IFN gamma production (Aguilar-Delfin, 2003)
2. Body's NO production, generated by L-arginine and IFN gamma (Stich, 1998 - although this was on *Babesia bovis*)
3. Increasing IL-12 (Aguilar-Delfin, 2003)
4. Regulation of IL-10 (Khan, 2019)
   - decrease in IL-10 stops the suppression of INF gamma and TNF alpha
   - increases production of NO from the macrophage and increases IL-12

https://montkush.com/6-benefits-and-uses-of-cbd-oil-plus-potential-side-effects/

Goals for Successful Resolution of Babesia

I. Immune system/cytokine modulation

II. Organ support and protection

III. Anti-Babesial herbs

Immune Modulation: Th1 & Th2

***Withania somnifera*/Ashwagandha**

- Counteracts the exact modulation of the immune system that **tick saliva** and **protozoa** initiate and maintain to keep infection going (Bani, 2006)

Astragalus membranaceus

- Inhibits several of the cytokines that cause Th2 dominence and contribute to inhibition of NO production (chen, 2014)

Immune Modulation: Decrease IL-10, IL-4 and TGF-beta

- IL-10 suppressors
  - ***Glycyrrhiza glabra* - licorice** (Luo, 2015)
  - ***Silybum* - milk thistle** (Wilasrusmee, 2002)
  - ***Cannabis sativa*** (Al-Ghezi, 2019)
  - ***Scutellaria baicalensis* - Chinese skullcap** (Bao, 2019)
  - ***Artemisia spp*** (Kim, 2021)
  - ***Withania somnifera* - Ashwagandha** (Saggam, 2021)
- IL-4 suppressors
  - ***Astragalus*** (Cui, 2018)
  - ***Glycyrrhiza*** (Richard, 2021)
- TGF-beta inhibitors
  - ***Artemisia spp*** (Jung, 2023)
  - ***Astragalus spp*** (Wei, 2020)
  - ***Schisandra chinensis*** (Chen, 2017)
  - ***Salvia miltiorrhiza*** (Wu, 2018)
  - ***Scutellaria spp*** (Bokhari, 2015)

Immune Modulation, cont'd

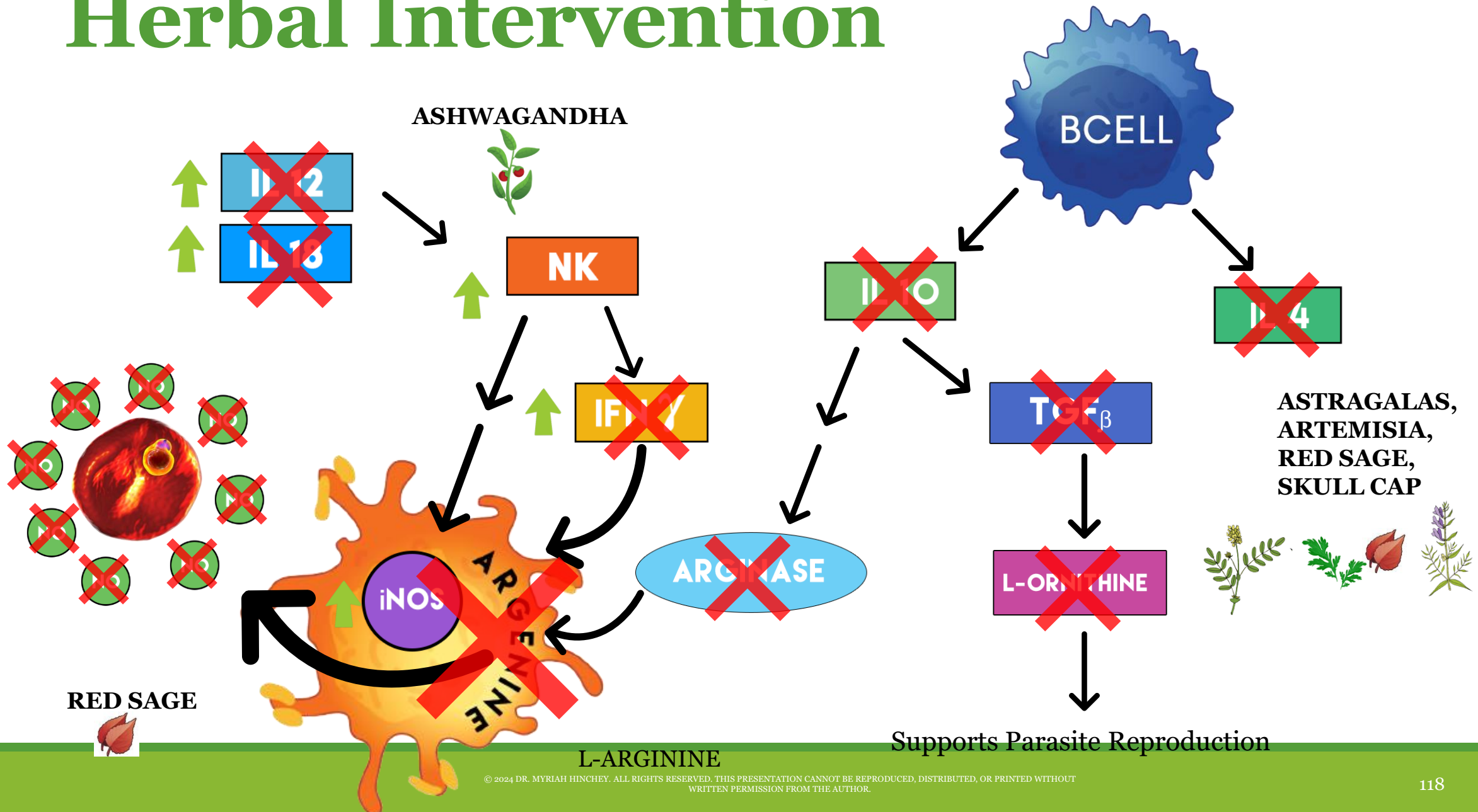
Inhibit generation of arginase to increase NO

- Arginase inhibitors
  - ***Panax ginseng*** (Shin, 2013)
  - ***Scutellaria baicalensis*** (Kim, 2013)
  - ***EGCG*** (dos Reis, 2013)

Increase IL-12, IL-18, INF- gamma, NO

- Inhibition of IL-10 (above)
- IL-12 stimulators
  - ***Eleutherococcus*** *senticosus* (Shin, 2013)
  - ***Astragalus spp*** (Lu, 2013)
- INF-gamma stimulators
  - ***Astragalus*** (Lu, 2013)
  - ***Grapefruit seed extract*** (Abdelkawy, 2017)

Herbal Intervention



Organ Support: RBCs

- Inhibit CDK and block RBC invasion
  - **Ginger** (Elkady, 2012)
  - ***Skullcap*** *(Guo, 2015)*
  - ***Artemisinin*** (Goda, 2021)
  - **Magnolia** (Lee, 2004)
  - **Licorice** (Lee, 2009)
- Protect RBC and relive anemia by increasing RBC numbers
  - ***Sida acuta*** (Ugwuezumba, 2018)
- Protect and increase NO levels for healthy vascular function
  - **L-arginine** (Boger, 2014)
    - most abundant in grass fed red meat (1/5th oz steak = 6 grams L-arginine!), spinach, walnuts, almonds
- Upregulate NOS and NO
  - **Red sage** (Jang, 2003)

Organ Support, cont'd

- **Endothelial cells**
- Normalize endothelial function and activates CDK inhibitors
  - ***Bidens pilosa*** (Wu, 2007)
- **Spleen**
- Upregulate CDK inhibition
  - **Red sage - *Salvia miltiorrhiza*** (Jung, 2020)
- **Liver**
- Upregulate CDK inhibitors
  - **Milk thistle - *Silybum marianum*** (Hogan, 2007)

Kill the Microbes: *Babesia spp.*

- ***Cryptolepis sanguinolenta*** (Zhang, 2021)
- ***Alchornia cordifolia*** (Zhang, 2021)
- ***Sida acuta*** (Chumpol, 2018)
- ***Bidens pilosa*** (Geissburger, 1991)
- ***Artemisia spp*** (Zhang, 2021)

frontiers in Cellular and Infection Microbiology

Front Cell Infect Microbiol. 2021; 11: 624745.
Published online 2021 Mar 8. doi: 10.3389/fcimb.2021.624745

PMCID: PMC7982592
PMID: 33763384

Botanical Medicines Cryptolepis sanguinolenta, Artemisia annua, Scutellaria baicalensis, Polygonum cuspidatum, and Alchornea cordifolia Demonstrate Inhibitory Activity Against Babesia duncani

Yumin Zhang,[1] Hector Alvarez-Manzo,[1] Jacob Leone,[2] Sunjya Schweig,[3] and Ying Zhang[4,*]

▸ Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Table 1

Evaluation of a panel of 46 herbal medicines at 0.01% (v/v) for inhibitory activity against *B. duncani* after 3 days of incubation.

Product Names	***Plants***	**Inhibition (%)**
Chinese Skullcap (90% EE)	*Scutellaria baicalensis*	84
Cryptolepis (90% EE)	*Cryptolepis sanguinolenta*	80
Cryptolepis (60% EE)	*Cryptolepis sanguinolenta*	70
Chinese Skullcap (60% EE)	*Scutellaria baicalensis*	68
Japanese knotweed (60% EE)	*Polygonum cuspidatum*	59
Sweet wormwood (30% EE)	*Artemisia annua*	58
Alchornea	*Alchornea cordifolia*	54
Japanese knotweed (90% EE)	*Polygonum cuspidatum*	42
Andrographis (90% EE)	*Andrographis paniculata*	37
Andrographis (60% EE)	*Andrographis paniculata*	36
Sweet wormwood (60% EE)	*Artemisia annua*	35
Andrographis (30% EE)	*Andrographis paniculata*	34
Cistus	*Cistus incanus*	34

Zhang, Y., Leone, J., Schweig, S., & Zhang, Y. (2021). Botanical Medicines Cryptolepis sanguinolenta, Artemisia annua, Scutellaria baicalensis, Polygonum cuspidatum, and Alchornea cordifolia Demonstrate Inhibitory Activity Against Babesia duncani. *Frontiers in Cellular and Infection Microbiology, 11*, 624745. https://doi.org/10.3389/fcimb.2021.624745

Babesia *Sample* Herbal Protocol

- ***Cryptolepis sanguinolenta***: ¼-½ tsp tid
- ***Alchornea cordifolia***: ¼ tsp tid
- ***Sida acuta***: ¼ tsp tid
- ***Artemisia annua***: ¼ tsp tid (or 200mg tid)
- ***Withania somnifera:*** *¼- ½ tsp tid*
- ***Salvia miltiorrhiza***: ½ tsp tid
- **L-arginine**: 2000 mg tid
- ***Astragalus membranaceus*****:** ¼- ½ tsp tid
- ***Silybum marianum***: 200 mg tid

Putting It All Together: Treatment for *Borrelia spp.* and *Babesia spp.*

Modulate Galactin-3: **Modified Citrus Pectin**

Balance Th1-Th2: **Ashwagandha, Astragalus**

Give back innate ability to destroy organisms via NO: ***Salvia miltiorrhiza***

Inflammatory cytokine cascade modulation: ***Polygonum cuspidatum***, ***Scutellaria baicalensis***, ***Salvia miltiorrhiza***

Protect endothelial cells: ***Polygonum cuspidatum***

Increase NK cells: ***Uncaria tomentosa***

Proven anti-microbials: **Cryptolepis**, **Sweet Annie, Teasel, Black walnut**

Antivirals: **Houttuynia**, ***Scutellaria baicalensis***, **Isatis**

Pre and probiotics

Detox support, replenish deficient micronutrients, anti-inflammatory diet, stress reduction, sleep etc.

Proprietary image created by Myriah Hinchey, 2023

Understand....

The Infection

Understand how the infectious organism thrives in the body

The Terrain

Understand how the patient's circumstances are making the body hospitable to infection

The Treatment

Understand the MOAs of the medications, herbs, and nutraceuticals available to you

... then you can create an intelligent, effective treatment plan!

Roadmap

Re-check, Wean, Remain

Once symptom free for 2 months, Re-check all labs that were abnormal. If normal – wean off protocol in the reverse order. Remain on the basic nutrients still needed for optimal health; retest food sensitivities and micronutrient levels.

Add Killers

Add in proven killers of virus, bacteria, parasites, mold, and fungus
Continue steps 1- 3.

Monitor Progress

Monitor progress every 8 weeks – looking for 25%
improvement by 90 days on full treatment protocol – treat until patient has been sx free for 2 solid months. Have patient fill out check list at every apt and rate the severity and frequency of sx at each apt. Repeat abnormal labs as medically necessary or 6-9 months for objective progress

Balance and rebuild

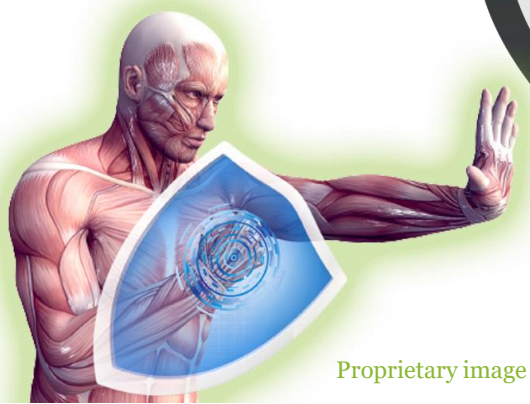
Add in herbs to shift cytokine cascade – balance T1- T2; increase NK cells; stop migration through CT, add binders & continue with steps 1-2.
Reminder of lifestyle (diet, sleep, stress, gratitude, movement)

Eliminate & Replenish

Eliminate all food allergies and sensitivities, replace def nutrients, work on routes of elimination (lungs, skin, colon, kidneys), gut healing,
probiotics, sleep, water, stress, positive thinking, gentle movement,
sunlight, gratitude. Continue anti-inflammatory diet.

Test and Address Lifestyle

Test for: Food sensitivities, Mold, Fungal, Lyme co-infections, Virus, Nutrient Deficiencies, MTHFR, Hormones, Organ Function, Gut Function, Dysbiosis, Histamine, Inflammatory Markers, and Immune Markers. Start anti-inflammatory diet. Address Nutrition, sleep, stress, gratitude, movement



References

Understanding the Spread of Borrelia Infection

1. Aounallah, H., Bensaoud, C., M'ghirbi, Y., Faria, F., Chmelar, J. I., & Kotsyfakis, M. (2020). Tick Salivary Compounds for Targeted Immunomodulatory Therapy. *Frontiers in immunology*, *11*, 583845. https://doi.org/10.3389/fimmu.2020.583845
2. Anderson C, Brissette CA. The Brilliance of Borrelia: Mechanisms of Host Immune Evasion by Lyme Disease-Causing Spirochetes. Pathogens. 2021 Mar 2;10(3):281. doi: 10.3390/pathogens10030281. PMID: 33801255; PMCID: PMC8001052.
3. Cotté, V., Sabatier, L., Schnell, G., Carmi-Leroy, A., Rousselle, J. C., Arsène-Ploetze, F., Malandrin, L., Sertour, N., Namane, A., Ferquel, E., & Choumet, V. (2014). Differential expression of Ixodes ricinus salivary gland proteins in the presence of the Borrelia burgdorferi sensu lato complex. Journal of proteomics, 96, 29–43. https://doi.org/10.1016/j.jprot.2013.10.033

Treatment of Lyme

3. Rupprecht, T. A., Koedel, U., Fingerle, V., & Pfister, H. W. (2008). The pathogenesis of lyme neuroborreliosis: from infection to inflammation. Molecular medicine (Cambridge, Mass.), 14(3-4), 205–212. https://doi.org/10.2119/2007-00091.Rupprecht
4. Quentin Bernard, Alexis A. Smith, Xiuli Yang, Juraj Koci, Shelby D. Foor, Sarah D. Cramer, Xuran Zhuang, Jennifer E. Dwyer, Yi-Pin Lin, Emmanuel F. Mongodin, Adriana Marques, John M. Leong, Juan Anguita, Utpal Pal. Plasticity in early immune evasion strategies of a bacterial pathogen. Proceedings of the National Academy of Sciences, 2018; 201718595 DOI: 10.1073/pnas.1718595115
5. Sahay, B., Singh, A., Gnanamani, A., Patsey, R. L., Blalock, J. E., & Sellati, T. J. (2011). CD14 signaling reciprocally controls collagen deposition and turnover to regulate the development of lyme arthritis. The American journal of pathology, 178(2), 724–734. https://doi.org/10.1016/j.ajpath.2010.10.025
6. Skare, J. T., & Garcia, B. L. (2020). Complement Evasion by Lyme Disease Spirochetes. Trends in microbiology, 28(11), 889–899. https://doi.org/10.1016/j.tim.2020.05.004
7. Horowitz, H. W., Dworkin, B., Forseter, G., Nadelman, R. B., Connolly, C., Luciano, B. B., Nowakowski, J., O'Brien, T. A., Calmann, M., & Wormser, G. P. (1996). Liver function in early Lyme disease. Hepatology (Baltimore, Md.), 23(6), 1412–1417. https://doi.org/10.1002/hep.510230617
8. Smith, A. , Oertle, J. , Warren, D. and Prato, D. (2015) Chronic Lyme Disease Complex and Its Commonly Undiagnosed Primary and Secondary Co-Infections. Open Journal of Medical Microbiology, 5, 143-158. doi: 10.4236/ojmm.2015.53018.

Initial Stages of Infection

9. Schwartz, D. J., Langdon, A. E., & Dantas, G. (2020). Understanding the impact of antibiotic perturbation on the human microbiome. *Genome medicine*, *12*(1), 82. https://doi.org/10.1186/s13073-020-00782-x
10. Aleman, R. S., Moncada, M., & Aryana, K. J. (2023). Leaky Gut and the Ingredients That Help Treat It: A Review. *Molecules (Basel, Switzerland)*, *28*(2), 619. https://doi.org/10.3390/molecules28020619
11. Björnsson E. S. (2017). Drug-induced liver injury due to antibiotics. *Scandinavian journal of gastroenterology*, *52*(6-7), 617–623. https://doi.org/10.1080/00365521.2017.1291719
12. Basolo, A., Hohenadel, M., Ang, Q. Y., Piaggi, P., Heinitz, S., Walter, M., Walter, P., Parrington, S., Trinidad, D. D., von Schwartzenberg, R. J., Turnbaugh, P. J., & Krakoff, J. (2020). Effects of underfeeding and oral vancomycin on gut microbiome and nutrient absorption in humans. *Nature medicine*, *26*(4), 589–598. https://doi.org/10.1038/s41591-020-0801-z
13. Sharma, B., Brown, A. V., Matluck, N. E., Hu, L. T., & Lewis, K. (2015). Borrelia burgdorferi, the Causative Agent of Lyme Disease, Forms Drug-Tolerant Persister Cells. *Antimicrobial agents and chemotherapy*, *59*(8), 4616–4624. https://doi.org/10.1128/AAC.00864-15
14. Antonara, S., Ristow, L., & Coburn, J. (2011). Adhesion mechanisms of Borrelia burgdorferi. Advances in experimental medicine and biology, 715, 35–49. https://doi.org/10.1007/978-94-007-0940-9_3
15. Grab, D. J., Perides, G., Dumler, J. S., Kim, K. J., Park, J., Kim, Y. V., Nikolskaia, O., Choi, K. S., Stins, M. F., & Kim, K. S. (2005). Borrelia burgdorferi, host-derived proteases, and the blood-brain barrier. Infection and immunity, 73(2), 1014–1022. https://doi.org/10.1128/IAI.73.2.1014-1022.2005
16. Hajnická, V., Kocáková, P., Sláviková, M., Slovák, M., Gasperík, J., Fuchsberger, N., & Nuttall, P. A. (2001). Anti-interleukin-8 activity of tick salivary gland extracts. Parasite immunology, 23(9), 483–489. https://doi.org/10.1046/j.1365-3024.2001.00403.x
17. Anguita, J., Persing, D. H., Rincon, M., Barthold, S. W., & Fikrig, E. (1996). Effect of anti-interleukin 12 treatment on murine lyme borreliosis. The Journal of clinical investigation, 97(4), 1028–1034. https://doi.org/10.1172/JCI118494

Initial Stages of Infection

17. Defosse, D. L., & Johnson, R. C. (1992). In vitro and in vivo induction of tumor necrosis factor alpha by Borrelia burgdorferi. Infection and immunity, 60(3), 1109–1113. https://doi.org/10.1128/iai.60.3.1109-1113.1992

18. Dame, T. M., Orenzoff, B. L., Palmer, L. E., & Furie, M. B. (2007). IFN-gamma alters the response of Borrelia burgdorferi-activated endothelium to favor chronic inflammation. Journal of immunology (Baltimore, Md. : 1950), 178(2), 1172–1179. https://doi.org/10.4049/jimmunol.178.2.1172

19. Benedikz, E. K., Bailey, D., Cook, C., Gonçalves-Carneiro, D., Buckner, M., Blair, J., Wells, T. J., Fletcher, N. F., Goodall, M., Flores-Langarica, A., Kingsley, R. A., Madsen, J., Teeling, J., Johnston, S. L., MacLennan, C. A., Balfe, P., Henderson, I. R., Piddock, L., Cunningham, A. F., & McKeating, J. A. (2019). Bacterial flagellin promotes viral entry via an NF-kB and Toll Like Receptor 5 dependent pathway. Scientific reports, 9(1), 7903. https://doi.org/10.1038/s41598-019-44263-7

20. Kanarek, N., London, N., Schueler-Furman, O., & Ben-Neriah, Y. (2010). Ubiquitination and degradation of the inhibitors of NF-kappaB. Cold Spring Harbor perspectives in biology, 2(2), a000166. https://doi.org/10.1101/cshperspect.a000166

21. Parthasarathy, G., & Philipp, M. T. (2014). The MEK/ERK pathway is the primary conduit for Borrelia burgdorferi-induced inflammation and P53-mediated apoptosis in oligodendrocytes. Apoptosis : an international journal on programmed cell death, 19(1), 76–89. https://doi.org/10.1007/s10495-013-0913-8

22. Yoon, J. Y., Kim, J. H., Baek, K. S., Kim, G. S., Lee, S. E., Lee, D. Y., Choi, J. H., Kim, S. Y., Park, H. B., Sung, G. H., Lee, K. R., Cho, J. Y., & Noh, H. J. (2015). A direct protein kinase B-targeted anti-inflammatory activity of cordycepin from artificially cultured fruit body of Cordyceps militaris. Pharmacognosy magazine, 11(43), 477–485. https://doi.org/10.4103/0973-1296.160454

23. Li, X. X., Zheng, X., Liu, Z., Xu, Q., Tang, H., Feng, J., Yang, S., Vong, C. T., Gao, H., & Wang, Y. (2020). Cryptotanshinone from Salvia miltiorrhiza Bunge (Danshen) inhibited inflammatory responses via TLR4/MyD88 signaling pathway. Chinese medicine, 15, 20. https://doi.org/10.1186/s13020-020-00303-3

Initial Stages of Infection

20. Kim, J. H., Bae, C. H., Park, S. Y., Lee, S. J., & Kim, Y. (2010). Uncaria rhynchophylla inhibits the production of nitric oxide and interleukin-1β through blocking nuclear factor κB, Akt, and mitogen-activated protein kinase activation in macrophages. Journal of medicinal food, 13(5), 1133–1140. https://doi.org/10.1089/jmf.2010.1128
21. Dong, N., Li, X., Xue, C., Zhang, L., Wang, C., Xu, X., & Shan, A. (2020). Astragalus polysaccharides alleviates LPS-induced inflammation via the NF-κB/MAPK signaling pathway. Journal of cellular physiology, 235(7-8), 5525–5540. https://doi.org/10.1002/jcp.29452
22. Park, S. J., Jang, H.-J., Hwang, I.-H., Kim, J. M., Jo, E., Lee, M.-G., Jang, I.-S., & Joo, J. C. (2018). Cordyceps militaris Extract Inhibits the NF-κB pathway and Induces Apoptosis through MKK7-JNK Signaling Activation in TK-10 Human Renal Cell Carcinoma. Natural Product Communications. https://doi.org/10.1177/1934578X1801300422
23. Shin, J. I., Jeon, Y. J., Lee, S., Lee, Y. G., Kim, J. B., Kwon, H. C., Kim, S. H., Kim, I., Lee, K., & Han, Y. S. (2018). Apoptotic and Anti-Inflammatory Effects of Eupatorium japonicum Thunb. in Rheumatoid Arthritis Fibroblast-Like Synoviocytes. BioMed research international, 2018, 1383697. https://doi.org/10.1155/2018/1383697
24. Lee, H. J., Seo, H. S., Kim, G. J., Jeon, C. Y., Park, J. H., Jang, B. H., Park, S. J., Shin, Y. C., & Ko, S. G. (2013). Houttuynia cordata Thunb inhibits the production of pro-inflammatory cytokines through inhibition of the NFκB signaling pathway in HMC-1 human mast cells. Molecular medicine reports, 8(3), 731–736. https://doi.org/10.3892/mmr.2013.1585

Initial Stages of Infection

25. Park, S. Y., Jin, M. L., Kang, N. J., Park, G., & Choi, Y. W. (2017). Anti-inflammatory effects of novel polygonum multiflorum compound via inhibiting NF-κB/MAPK and upregulating the Nrf2 pathways in LPS-stimulated microglia. Neuroscience letters, 651, 43–51. https://doi.org/10.1016/j.neulet.2017.04.057
26. Bulugonda, R., kumar, K., Gangappa, D. et al. Mangiferin from Pueraria tuberosa reduces inflammation via inactivation of NLRP3 inflammasome. Sci Rep 7, 42683 (2017). https://doi.org/10.1038/srep42683
27. Cheung, D. W., Koon, C. M., Wat, E., Ko, C. H., Chan, J. Y., Yew, D. T., Leung, P. C., Chan, W. Y., Lau, C. B., & Fung, K. P. (2013). A herbal formula containing roots of Salvia miltiorrhiza (Danshen) and Pueraria lobata (Gegen) inhibits inflammatory mediators in LPS-stimulated RAW 264.7 macrophages through inhibition of nuclear factor κB (NFκB) pathway. Journal of ethnopharmacology, 145(3), 776–783. https://doi.org/10.1016/j.jep.2012.12.011
28. Li, J., Ma, J., Wang, K. S., Mi, C., Wang, Z., Piao, L. X., Xu, G. H., Li, X., Lee, J. J., & Jin, X. (2016). Baicalein inhibits TNF-α-induced NF-κB activation and expression of NF-κB-regulated target gene products. Oncology reports, 36(5), 2771–2776. https://doi.org/10.3892/or.2016.5108
29. Singh, D., Aggarwal, A., Maurya, R., & Naik, S. (2007). Withania somnifera inhibits NF-kappaB and AP-1 transcription factors in human peripheral blood and synovial fluid mononuclear cells. Phytotherapy research : PTR, 21(10), 905–913. https://doi.org/10.1002/ptr.2180

Initial Stages of Infection

30. Watanabe, H., Yamada, Y., & Kimata, K. (1998). Roles of aggrecan, a large chondroitin sulfate proteoglycan, in cartilage structure and function. Journal of biochemistry, 124(4), 687–693. https://doi.org/10.1093/oxfordjournals.jbchem.a022166
31. Russell, T. M., & Johnson, B. J. (2013). Lyme disease spirochaetes possess an aggrecan-binding protease with aggrecanase activity. Molecular microbiology, 90(2), 228–240. https://doi.org/10.1111/mmi.12276
32. Bushra Hassan Marouf, "Effect of Resveratrol on Serum Levels of Type II Collagen and Aggrecan in Patients with Knee Osteoarthritis: A Pilot Clinical Study", BioMed Research International, vol. 2021, Article ID 3668568, 9 pages, 2021. https://doi.org/10.1155/2021/3668568
33. Yotsawimonwat, S., Rattanadechsakul, J., Rattanadechsakul, P., & Okonogi, S. (2010). Skin improvement and stability of Echinacea purpurea dermatological formulations. International journal of cosmetic science, 32(5), 340–346. https://doi.org/10.1111/j.1468-2494.2009.00559.x
34. Machiah, D. K., Girish, K. S., & Gowda, T. V. (2006). A glycoprotein from a folk medicinal plant, Withania somnifera, inhibits hyaluronidase activity of snake venoms. Comparative biochemistry and physiology. Toxicology & pharmacology : CBP, 143(2), 158–161. https://doi.org/10.1016/j.cbpc.2006.01.006
35. Kolar, S. L., Kyme, P., Tseng, C. W., Soliman, A., Kaplan, A., Liang, J., Nizet, V., Jiang, D., Murali, R., Arditi, M., Underhill, D. M., & Liu, G. Y. (2015). Group B Streptococcus Evades Host Immunity by Degrading Hyaluronan. Cell host & microbe, 18(6), 694–704. https://doi.org/10.1016/j.chom.2015.11.001

All Stages of Infection

36. Sahay, B., Bashant, K., Nelson, N., Patsey, R. L., Gadila, S. K., Boohaker, R., Verma, A., Strle, K., & Sellati, T. J. (2018). Induction of Interleukin 10 by Borrelia burgdorferi Is Regulated by the Action of CD14-Dependent p38 Mitogen-Activated Protein Kinase and cAMP-Mediated Chromatin Remodeling. Infection and immunity, 86(4), e00781-17. https://doi.org/10.1128/IAI.00781-17
37. Collins, C., Wolfe, J., Roessner, K., Shi, C., Sigal, L. H., & Budd, R. C. (2005). Lyme arthritis synovial gammadelta T cells instruct dendritic cells via fas ligand. Journal of immunology (Baltimore, Md. : 1950), 175(9), 5656–5665. https://doi.org/10.4049/jimmunol.175.9.5656
38. Johnson, G. L., & Lapadat, R. (2002). Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science (New York, N.Y.), 298(5600), 1911–1912. https://doi.org/10.1126/science.1072682
39. Han, J. Y., Im, J., Choi, J. N., Lee, C. H., Park, H. J., Park, D. K., Yun, C. H., & Han, S. H. (2010). Induction of IL-8 expression by Cordyceps militaris grown on germinated soybeans through lipid rafts formation and signaling pathways via ERK and JNK in A549 cells. Journal of ethnopharmacology, 127(1), 55–61. https://doi.org/10.1016/j.jep.2009.09.051
40. Kim, H. N., Kim, Y. R., Jang, J. Y., Choi, Y. W., Baek, J. U., Hong, J. W., Choi, Y. H., Shin, H. K., & Choi, B. T. (2013). Neuroprotective effects of Polygonum multiflorum extract against glutamate-induced oxidative toxicity in HT22 hippocampal cells. Journal of ethnopharmacology, 150(1), 108–115. https://doi.org/10.1016/j.jep.2013.08.014
41. Kim, J. H., Woo, J. H., Kim, H. M., Oh, M. S., Jang, D. S., & Choi, J. H. (2017). Anti-Endometriotic Effects of Pueraria Flower Extract in Human Endometriotic Cells and Mice. Nutrients, 9(3), 212. https://doi.org/10.3390/nu9030212

All Stages of Infection

42. Pan, T. L., Wang, P. W., Leu, Y. L., Wu, T. H., & Wu, T. S. (2012). Inhibitory effects of Scutellaria baicalensis extract on hepatic stellate cells through inducing G2/M cell cycle arrest and activating ERK-dependent apoptosis via Bax and caspase pathway. Journal of ethnopharmacology, 139(3), 829–837. https://doi.org/10.1016/j.jep.2011.12.028
43. Xie, Q., Yang, Y., Wang, Z., Chen, F., Zhang, A., & Liu, C. (2014). Resveratrol-4-O-D-(2'-galloyl)-glucopyranoside isolated from Polygonum cuspidatum exhibits anti-hepatocellular carcinoma viability by inducing apoptosis via the JNK and ERK pathway. Molecules (Basel, Switzerland), 19(2), 1592–1602. https://doi.org/10.3390/molecules19021592
44. Huang, H. H., Shao, Z. H., Li, C. Q., Vanden Hoek, T. L., & Li, J. (2014). Baicalein protects cardiomyocytes against mitochondrial oxidant injury associated with JNK inhibition and mitochondrial Akt activation. The American journal of Chinese medicine, 42(1), 79–94. https://doi.org/10.1142/S0192415X14500050
45. Das, G., Shin, H. S., Leyva-Gómez, G., Prado-Audelo, M., Cortes, H., Singh, Y. D., Panda, M. K., Mishra, A. P., Nigam, M., Saklani, S., Chaturi, P. K., Martorell, M., Cruz-Martins, N., Sharma, V., Garg, N., Sharma, R., & Patra, J. K. (2021). Cordyceps spp.: A Review on Its Immune-Stimulatory and Other Biological Potentials. Frontiers in pharmacology, 11, 602364. https://doi.org/10.3389/fphar.2020.602364
46. Zhang, L., Wang, X., Wang, R., Zheng, X., Li, N., Li, H., Cao, X., Zhou, B., Lin, Y., & Yang, L. (2017). Baicalin potentiates TRAIL-induced apoptosis through p38 MAPK activation and intracellular reactive oxygen species production. Molecular medicine reports, 16(6), 8549–8555. https://doi.org/10.3892/mmr.2017.7633

All Stages of Infection

47. Wichers, M. C., Koek, G. H., Robaeys, G., Verkerk, R., Scharpé, S., & Maes, M. (2005). IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. Molecular psychiatry, 10(6), 538–544. https://doi.org/10.1038/sj.mp.4001600
48. Lin, C. J., Lin, H. J., Chen, T. H., Hsu, Y. A., Liu, C. S., Hwang, G. Y., & Wan, L. (2015). Polygonum cuspidatum and its active components inhibit replication of the influenza virus through toll-like receptor 9-induced interferon beta expression. PloS one, 10(2), e0117602. https://doi.org/10.1371/journal.pone.0117602
49. Błach-Olszewska, Z., Jatczak, B., Rak, A., Lorenc, M., Gulanowski, B., Drobna, A., & Lamer-Zarawska, E. (2008). Production of cytokines and stimulation of resistance to viral infection in human leukocytes by Scutellaria baicalensis flavones. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research, 28(9), 571–581. https://doi.org/10.1089/jir.2008.0125
50. Zhang XD, Xu DZ, Li JH, et al. [Study on the immunocompetence of polysaccharide extracted from root of Salvia miltiorrhiza]. Zhong yao cai = Zhongyaocai = Journal of Chinese Medicinal Materials. 2012 Jun;35(6):949-952. PMID: 23236833.
51. Love, A. C., Schwartz, I., & Petzke, M. M. (2015). Induction of indoleamine 2,3-dioxygenase by Borrelia burgdorferi in human immune cells correlates with pathogenic potential. Journal of leukocyte biology, 97(2), 379–390. https://doi.org/10.1189/jlb.4A0714-339R

All Stages of Infection

52. Chen, S., Corteling, R., Stevanato, L., & Sinden, J. (2012). Natural inhibitors of indoleamine 3,5-dioxygenase induced by interferon-gamma in human neural stem cells. Biochemical and biophysical research communications, 429(1-2), 117–123. https://doi.org/10.1016/j.bbrc.2012.10.009
53. Jenny, M., Wondrak, A., Zvetkova, E., Tram, N. T., Phi, P. T., Schennach, H., Culig, Z., Ueberall, F., & Fuchs, D. (2011). Crinum latifolium leave extracts suppress immune activation cascades in peripheral blood mononuclear cells and proliferation of prostate tumor cells. Scientia pharmaceutica, 79(2), 323–335. https://doi.org/10.3797/scipharm.1011-13
54. Heyes, M. P., Saito, K., Crowley, J. S., Davis, L. E., Demitrack, M. A., Der, M., Dilling, L. A., Elia, J., Kruesi, M. J., & Lackner, A. (1992). Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. Brain : a journal of neurology, 115 (Pt 5), 1249–1273. https://doi.org/10.1093/brain/115.5.1249
55. Basile, A. S., Saito, K., al-Mardini, H., Record, C. O., Hughes, R. D., Harrison, P., Williams, R., Li, Y., & Heyes, M. P. (1995). The relationship between plasma and brain quinolinic acid levels and the severity of hepatic encephalopathy. Gastroenterology, 108(3), 818–823. https://doi.org/10.1016/0016-5085(95)90456-5

All Stages of Infection

52. Chen, S., Corteling, R., Stevanato, L., & Sinden, J. (2012). Natural inhibitors of indoleamine 3,5-dioxygenase induced by interferon-gamma in human neural stem cells. Biochemical and biophysical research communications, 429(1-2), 117–123. https://doi.org/10.1016/j.bbrc.2012.10.009
53. Jenny, M., Wondrak, A., Zvetkova, E., Tram, N. T., Phi, P. T., Schennach, H., Culig, Z., Ueberall, F., & Fuchs, D. (2011). Crinum latifolium leave extracts suppress immune activation cascades in peripheral blood mononuclear cells and proliferation of prostate tumor cells. Scientia pharmaceutica, 79(2), 323–335. https://doi.org/10.3797/scipharm.1011-13
54. Heyes, M. P., Saito, K., Crowley, J. S., Davis, L. E., Demitrack, M. A., Der, M., Dilling, L. A., Elia, J., Kruesi, M. J., & Lackner, A. (1992). Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. Brain : a journal of neurology, 115 (Pt 5), 1249–1273. https://doi.org/10.1093/brain/115.5.1249
55. Basile, A. S., Saito, K., al-Mardini, H., Record, C. O., Hughes, R. D., Harrison, P., Williams, R., Li, Y., & Heyes, M. P. (1995). The relationship between plasma and brain quinolinic acid levels and the severity of hepatic encephalopathy. Gastroenterology, 108(3), 818–823. https://doi.org/10.1016/0016-5085(95)90456-5

All Stages of Infection

59. Vega-Naredo, I., Poeggeler, B., Sierra-Sánchez, V., Caballero, B., Tomás-Zapico, C., Alvarez-García, O., Tolivia, D., Rodríguez-Colunga, M. J., & Coto-Montes, A. (2005). Melatonin neutralizes neurotoxicity induced by quinolinic acid in brain tissue culture. Journal of pineal research, 39(3), 266–275. https://doi.org/10.1111/j.1600-079X.2005.00243.x
60. Santamaría, A., Salvatierra-Sánchez, R., Vázquez-Román, B., Santiago-López, D., Villeda-Hernández, J., Galván-Arzate, S., Jiménez-Capdeville, M. E., & Ali, S. F. (2003). Protective effects of the antioxidant selenium on quinolinic acid-induced neurotoxicity in rats: in vitro and in vivo studies. Journal of neurochemistry, 86(2), 479–488. https://doi.org/10.1046/j.1471-4159.2003.01857.x
61. Grygorczuk, S., Pancewicz, S., Zajkowska, J., Kondrusik, M., Rwierzbińska, R., & Hermanowska-Szpakowicz, T. (2004). Concentrations of macrophage inflammatory proteins MIP-1alpha and MIP-1beta and interleukin 8 (il-8) in lyme borreliosis. Infection, 32(6), 350–355. https://doi.org/10.1007/s15010-004-3110-4
62. Fang, J., Wang, W., Hu, Y., Feng, D., & Tang, J. (2005). Influence of Radix Isatidis on the endotoxin-induced release of TNF-alpha and IL-8 from HL-60 cells. Journal of Huazhong University of Science and Technology. Medical sciences = Hua zhong ke ji da xue xue bao. Yi xue Ying De wen ban = Huazhong keji daxue xuebao. Yixue Yingdewen ban, 25(5), 546–548. https://doi.org/10.1007/BF02896013
63. Zhou, N., Yang, X., Huang, A., & Chen, Z. (2021). The Potential Mechanism of N-acetylcysteine in Treating COVID-19. Current pharmaceutical biotechnology, 22(12), 1584–1590. https://doi.org/10.2174/1389201021999201228212043

All Stages of Infection

64. Quagliariello, V., Berretta, M., Buccolo, S., Iovine, M., Paccone, A., Cavalcanti, E., Taibi, R., Montopoli, M., Botti, G., & Maurea, N. (2021). Polydatin Reduces Cardiotoxicity and Enhances the Anticancer Effects of Sunitinib by Decreasing Pro-Oxidative Stress, Pro-Inflammatory Cytokines, and NLRP3 Inflammasome Expression. Frontiers in oncology, 11, 680758. https://doi.org/10.3389/fonc.2021.680758
65. Di Caprio, R., Lembo, S., Di Costanzo, L., Balato, A., & Monfrecola, G. (2015). Anti-inflammatory properties of low and high doxycycline doses: an in vitro study. Mediators of inflammation, 2015, 329418. https://doi.org/10.1155/2015/329418
66. Miller, L. C., Isa, S., Vannier, E., Georgilis, K., Steere, A. C., & Dinarello, C. A. (1992). Live Borrelia burgdorferi preferentially activate interleukin-1 beta gene expression and protein synthesis over the interleukin-1 receptor antagonist. The Journal of clinical investigation, 90(3), 906–912. https://doi.org/10.1172/JCI115966
67. Molina-Holgado, E., Ortiz, S., Molina-Holgado, F., & Guaza, C. (2000). Induction of COX-2 and PGE(2) biosynthesis by IL-1beta is mediated by PKC and mitogen-activated protein kinases in murine astrocytes. British journal of pharmacology, 131(1), 152–159. https://doi.org/10.1038/sj.bjp.0703557
68. Simon L. S. (1999). Role and regulation of cyclooxygenase-2 during inflammation. The American journal of medicine, 106(5B), 37S–42S. https://doi.org/10.1016/s0002-9343(99)00115-1

All Stages of Infection

69. Hu, P., Chen, W., Bao, J., Jiang, L., & Wu, L. (2014). Cordycepin modulates inflammatory and catabolic gene expression in interleukin-1beta-induced human chondrocytes from advanced-stage osteoarthritis: an in vitro study. International journal of clinical and experimental pathology, 7(10), 6575–6584.
70. Chen, X., Han, R., Hao, P., Wang, L., Liu, M., Jin, M., Kong, D., & Li, X. (2018). Nepetin inhibits IL-1β induced inflammation via NF-κB and MAPKs signaling pathways in ARPE-19 cells. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 101, 87–93. https://doi.org/10.1016/j.biopha.2018.02.054
71. Liu, B., Li, S., Sui, X., Guo, L., Liu, X., Li, H., Gao, L., Cai, S., Li, Y., Wang, T., & Piao, X. (2018). Root Extract of Polygonum cuspidatum Siebold & Zucc. Ameliorates DSS-Induced Ulcerative Colitis by Affecting NF-kappaB Signaling Pathway in a Mouse Model via Synergistic Effects of Polydatin, Resveratrol, and Emodin. Frontiers in pharmacology, 9, 347. https://doi.org/10.3389/fphar.2018.00347
72. Zhu, X., Xie, M., Wang, K., Zhang, K., Gao, Y., Zhu, L., & Zhou, F. (2014). The effect of puerarin against IL-1β-mediated leukostasis and apoptosis in retinal capillary endothelial cells (TR-iBRB2). Molecular vision, 20, 1815–1823.
73. Ma, S., Zhang, D., Lou, H., Sun, L., & Ji, J. (2016). Evaluation of the anti-inflammatory activities of tanshinones isolated from Salvia miltiorrhiza var. alba roots in THP-1 macrophages. Journal of ethnopharmacology, 188, 193–199. https://doi.org/10.1016/j.jep.2016.05.018

All Stages of Infection

74. Hsieh, C. J., Hall, K., Ha, T., Li, C., Krishnaswamy, G., & Chi, D. S. (2007). Baicalein inhibits IL-1beta- and TNF-alpha-induced inflammatory cytokine production from human mast cells via regulation of the NF-kappaB pathway. Clinical and molecular allergy : CMA, 5, 5. https://doi.org/10.1186/1476-7961-5-5
75. Egecioglu, E., Anesten, F., Schéle, E., & Palsdottir, V. (2018). Interleukin-6 is important for regulation of core body temperature during long-term cold exposure in mice. Biomedical reports, 9(3), 206–212. https://doi.org/10.3892/br.2018.1118
76. Späth-Schwalbe, E., Born, J., Schrezenmeier, H., Bornstein, S. R., Stromeyer, P., Drechsler, S., Fehm, H. L., & Porzsolt, F. (1994). Interleukin-6 stimulates the hypothalamus-pituitary-adrenocortical axis in man. The Journal of clinical endocrinology and metabolism, 79(4), 1212–1214. https://doi.org/10.1210/jcem.79.4.7962296
77. Kimura, A., & Kishimoto, T. (2010). IL-6: regulator of Treg/Th17 balance. European journal of immunology, 40(7), 1830–1835. https://doi.org/10.1002/eji.201040391
78. Li, Y., Xiang, L. L., Miao, J. X., Miao, M. S., & Wang, C. (2021). Protective effects of andrographolide against cerebral ischemia-reperfusion injury in mice. International journal of molecular medicine, 48(4), 186. https://doi.org/10.3892/ijmm.2021.5019

All Stages of Infection

79. Lotts, T., Kabrodt, K., Hummel, J., Binder, D., Schellenberg, I., Ständer, S., & Agelopoulos, K. (2020). Isatis tinctoria L.-derived Petroleum Ether Extract Mediates Anti-inflammatory Effects via Inhibition of Interleukin-6, Interleukin-33 and Mast Cell Degranulation. Acta dermato-venereologica, 100(10), adv00131. https://doi.org/10.2340/00015555-3476
80. Shukla, R., Banerjee, S., & Tripathi, Y. B. (2018). Pueraria tuberosa extract inhibits iNOS and IL-6 through suppression of PKC-α and NF-kB pathway in diabetes-induced nephropathy. The Journal of pharmacy and pharmacology, 70(8), 1102–1112. https://doi.org/10.1111/jphp.12931
81. Jang, S. I., Jeong, S. I., Kim, K. J., Kim, H. J., Yu, H. H., Park, R., Kim, H. M., & You, Y. O. (2003). Tanshinone IIA from Salvia miltiorrhiza inhibits inducible nitric oxide synthase expression and production of TNF-alpha, IL-1beta and IL-6 in activated RAW 264.7 cells. Planta medica, 69(11), 1057–1059. https://doi.org/10.1055/s-2003-45157
82. Liu, L., Dong, Y., Shan, X., Li, L., Xia, B., & Wang, H. (2019). Anti-Depressive Effectiveness of Baicalin In Vitro and In Vivo. Molecules (Basel, Switzerland), 24(2), 326. https://doi.org/10.3390/molecules24020326
83. Conforti, C., Giuffrida, R., Zalaudek, I., & Di Meo, N. (2020). Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak. Dermatologic therapy, 33(4), e13437. https://doi.org/10.1111/dth.13437

All Stages of Infection

84. Dunn A. J. (2000). Cytokine activation of the HPA axis. Annals of the New York Academy of Sciences, 917, 608–617. https://doi.org/10.1111/j.1749-6632.2000.tb05426.x
85. Knobler, H., & Schattner, A. (2005). TNF-{alpha}, chronic hepatitis C and diabetes: a novel triad. QJM : monthly journal of the Association of Physicians, 98(1), 1–6. https://doi.org/10.1093/qjmed/hci001
86. Raffaele, S., Lombardi, M., Verderio, C., & Fumagalli, M. (2020). TNF Production and Release from Microglia via Extracellular Vesicles: Impact on Brain Functions. Cells, 9(10), 2145. https://doi.org/10.3390/cells9102145
87. Li, Y., He, S., Tang, J., Ding, N., Chu, X., Cheng, L., Ding, X., Liang, T., Feng, S., Rahman, S. U., Wang, X., & Wu, J. (2017). Andrographolide Inhibits Inflammatory Cytokines Secretion in LPS-Stimulated RAW264.7 Cells through Suppression of NF-κB/MAPK Signaling Pathway. Evidence-based complementary and alternative medicine : eCAM, 2017, 8248142. https://doi.org/10.1155/2017/8248142
88. Zhu, Z. Y., Chen, J., Si, C. L., Liu, N., Lian, H. Y., Ding, L. N., Liu, Y., & Zhang, Y. M. (2012). Immunomodulatory effect of polysaccharides from submerged cultured Cordyceps gunnii. Pharmaceutical biology, 50(9), 1103–1110. https://doi.org/10.3109/13880209.2012.658114
89. Chakravarty, A. K., Mazumder, T., & Chatterjee, S. N. (2011). Anti-Inflammatory Potential of Ethanolic Leaf Extract of Eupatorium adenophorum Spreng. Through Alteration in Production of TNF-α, ROS and Expression of Certain Genes. Evidence-based complementary and alternative medicine : eCAM, 2011, 471074. https://doi.org/10.1093/ecam/neq033

All Stages of Infection

90. Park, E., Kum, S., Wang, C., Park, S. Y., Kim, B. S., & Schuller-Levis, G. (2005). Anti-inflammatory activity of herbal medicines: inhibition of nitric oxide production and tumor necrosis factor-alpha secretion in an activated macrophage-like cell line. The American journal of Chinese medicine, 33(3), 415–424. https://doi.org/10.1142/S0192415X05003028
91. Wu, X., Deng, X., Wang, J., & Li, Q. (2020). Baicalin Inhibits Cell Proliferation and Inflammatory Cytokines Induced by Tumor Necrosis Factor α (TNF-α) in Human Immortalized Keratinocytes (HaCaT) Human Keratinocytes by Inhibiting the STAT3/Nuclear Factor kappa B (NF-κB) Signaling Pathway. Medical science monitor : international medical journal of experimental and clinical research, 26, e919392. https://doi.org/10.12659/MSM.919392
92. Peng, G. L., & Zhang, X. Y. (2007). Zhong xi yi jie he xue bao = Journal of Chinese integrative medicine, 5(1), 28–31. https://doi.org/10.3736/jcim20070106
93. Van Doren S. R. (2015). Matrix metalloproteinase interactions with collagen and elastin. Matrix biology : journal of the International Society for Matrix Biology, 44-46, 224–231. https://doi.org/10.1016/j.matbio.2015.01.005
94. Kang, D. G., Lee, H. J., Lee, C. J., & Park, J. S. (2018). Inhibition of the Expression of Matrix Metalloproteinases in Articular Chondrocytes by Resveratrol through Affecting Nuclear Factor-Kappa B Signaling Pathway. Biomolecules & therapeutics, 26(6), 560–567. https://doi.org/10.4062/biomolther.2018.132

All Stages of Infection

95. Cai, H., Li, J., Gu, B., Xiao, Y., Chen, R., Liu, X., Xie, X., & Cao, L. (2018). Extracts of Cordyceps sinensis inhibit breast cancer cell metastasis via down-regulation of metastasis-related cytokines expression. Journal of ethnopharmacology, 214, 106–112. https://doi.org/10.1016/j.jep.2017.12.012
96. Liu, Y., Ni, Y., Zhang, W., Sun, Y. E., Ma, Z., & Gu, X. (2017). N-acetyl-cysteine attenuates remifentanil-induced postoperative hyperalgesia via inhibiting matrix metalloproteinase-9 in dorsal root ganglia. Oncotarget, 8(10), 16988–17001. https://doi.org/10.18632/oncotarget.15217
97. Kim, J. M., Noh, E. M., Song, H. K., Lee, M., Lee, S. H., Park, S. H., Ahn, C. K., Lee, G. S., Byun, E. B., Jang, B. S., Kwon, K. B., & Lee, Y. R. (2017). Salvia miltiorrhiza extract inhibits TPA-induced MMP-9 expression and invasion through the MAPK/AP-1 signaling pathway in human breast cancer MCF-7 cells. Oncology letters, 14(3), 3594–3600. https://doi.org/10.3892/ol.2017.6638
98. Chen, H. M., Liou, S. F., Hsu, J. H., Chen, T. J., Cheng, T. L., Chiu, C. C., & Yeh, J. L. (2014). Baicalein inhibits HMGB1 release and MMP-2/-9 expression in lipopolysaccharide-induced cardiac hypertrophy. The American journal of Chinese medicine, 42(4), 785–797. https://doi.org/10.1142/S0192415X14500505
99. Cai, H., Li, J., Gu, B., Xiao, Y., Chen, R., Liu, X., Xie, X., & Cao, L. (2018). Extracts of Cordyceps sinensis inhibit breast cancer cell metastasis via down-regulation of metastasis-related cytokines expression. Journal of ethnopharmacology, 214, 106–112. https://doi.org/10.1016/j.jep.2017.12.012

All Stages of Infection

95. Cai, H., Li, J., Gu, B., Xiao, Y., Chen, R., Liu, X., Xie, X., & Cao, L. (2018). Extracts of Cordyceps sinensis inhibit breast cancer cell metastasis via down-regulation of metastasis-related cytokines expression. Journal of ethnopharmacology, 214, 106–112. https://doi.org/10.1016/j.jep.2017.12.012
96. Liu, Y., Ni, Y., Zhang, W., Sun, Y. E., Ma, Z., & Gu, X. (2017). N-acetyl-cysteine attenuates remifentanil-induced postoperative hyperalgesia via inhibiting matrix metalloproteinase-9 in dorsal root ganglia. Oncotarget, 8(10), 16988–17001. https://doi.org/10.18632/oncotarget.15217
97. Kim, J. M., Noh, E. M., Song, H. K., Lee, M., Lee, S. H., Park, S. H., Ahn, C. K., Lee, G. S., Byun, E. B., Jang, B. S., Kwon, K. B., & Lee, Y. R. (2017). Salvia miltiorrhiza extract inhibits TPA-induced MMP-9 expression and invasion through the MAPK/AP-1 signaling pathway in human breast cancer MCF-7 cells. Oncology letters, 14(3), 3594–3600. https://doi.org/10.3892/ol.2017.6638
98. Chen, H. M., Liou, S. F., Hsu, J. H., Chen, T. J., Cheng, T. L., Chiu, C. C., & Yeh, J. L. (2014). Baicalein inhibits HMGB1 release and MMP-2/-9 expression in lipopolysaccharide-induced cardiac hypertrophy. The American journal of Chinese medicine, 42(4), 785–797. https://doi.org/10.1142/S0192415X14500505=
99. Cai, H., Li, J., Gu, B., Xiao, Y., Chen, R., Liu, X., Xie, X., & Cao, L. (2018). Extracts of Cordyceps sinensis inhibit breast cancer cell metastasis via down-regulation of metastasis-related cytokines expression. Journal of ethnopharmacology, 214, 106–112. https://doi.org/10.1016/j.jep.2017.12.012
100. Noh, E. M., Kim, J. S., Hur, H., Park, B. H., Song, E. K., Han, M. K., Kwon, K. B., Yoo, W. H., Shim, I. K., Lee, S. J., Youn, H. J., & Lee, Y. R. (2009). Cordycepin inhibits IL-1beta-induced MMP-1 and MMP-3 expression in rheumatoid arthritis synovial fibroblasts. Rheumatology (Oxford, England), 48(1), 45–48. https://doi.org/10.1093/rheumatology/ken417

My Approach

101. Valenta, R., Hochwallner, H., Linhart, B., & Pahr, S. (2015). Food allergies: the basics. Gastroenterology, 148(6), 1120–31.e4. https://doi.org/10.1053/j.gastro.2015.02.006
102. Lu, C. Y., Shih, Y. L., Sun, L. C., Chuang, J. F., Ma, C. J., Chen, F. M., Wu, D. C., Hsieh, J. S., & Wang, J. Y. (2011). The inflammatory modulation effect of glutamine-enriched total parenteral nutrition in postoperative gastrointestinal cancer patients. The American surgeon, 77(1), 59–64.
103. Ramachandran, C., Wilk, B., Melnick, S. J., & Eliaz, I. (2017). Synergistic Antioxidant and Anti-Inflammatory Effects between Modified Citrus Pectin and Honokiol. Evidence-based complementary and alternative medicine : eCAM, 2017, 8379843. https://doi.org/10.1155/2017/8379843
104. Chaturvedi, V. K., Agarwal, S., Gupta, K. K., Ramteke, P. W., & Singh, M. P. (2018). Medicinal mushroom: boon for therapeutic applications. 3 Biotech, 8(8), 334. https://doi.org/10.1007/s13205-018-1358-0
105. Kieffer, D. A., Martin, R. J., & Adams, S. H. (2016). Impact of Dietary Fibers on Nutrient Management and Detoxification Organs: Gut, Liver, and Kidneys. Advances in nutrition (Bethesda, Md.), 7(6), 1111–1121. https://doi.org/10.3945/an.116.013219
106. Pastore, A., Federici, G., Bertini, E., & Piemonte, F. (2003). Analysis of glutathione: implication in redox and detoxification. Clinica chimica acta; international journal of clinical chemistry, 333(1), 19–39. https://doi.org/10.1016/s0009-8981(03)00200-6

My Approach

107. Pajares, M. A., & Pérez-Sala, D. (2018). Mammalian Sulfur Amino Acid Metabolism: A Nexus Between Redox Regulation, Nutrition, Epigenetics, and Detoxification. Antioxidants & redox signaling, 29(4), 408–452. https://doi.org/10.1089/ars.2017.7237
108. Parikh, M., Maddaford, T. G., Austria, J. A., Aliani, M., Netticadan, T., & Pierce, G. N. (2019). Dietary Flaxseed as a Strategy for Improving Human Health. Nutrients, 11(5), 1171. https://doi.org/10.3390/nu11051171
109. Ullah, R., Nadeem, M., Khalique, A., Imran, M., Mehmood, S., Javid, A., & Hussain, J. (2016). Nutritional and therapeutic perspectives of Chia (Salvia hispanica L.): a review. Journal of food science and technology, 53(4), 1750–1758. https://doi.org/10.1007/s13197-015-1967-0
110. Genuis, S. J., Birkholz, D., Ralitsch, M., & Thibault, N. (2010). Human detoxification of perfluorinated compounds. Public health, 124(7), 367–375. https://doi.org/10.1016/j.puhe.2010.03.002
111. Li, Y., Deng, S., Zhao, Y., Liu, L., & Zhao, R. (2017). Smilax glabra Rhizoma affects the pharmacokinetics and tissue distribution of methotrexate by increasing the P-glycoprotein mRNA expression in rats after oral administration. Molecular medicine reports, 16(5), 7633–7640. https://doi.org/10.3892/mmr.2017.7559
112. Ragg, R., Natalio, F., Tahir, M. N., Janssen, H., Kashyap, A., Strand, D., Strand, S., & Tremel, W. (2014). Molybdenum trioxide nanoparticles with intrinsic sulfite oxidase activity. ACS nano, 8(5), 5182–5189. https://doi.org/10.1021/nn501235j

My Approach

114. Feng, J., Leone, J., Schweig, S., & Zhang, Y. (2020). Evaluation of Natural and Botanical Medicines for Activity Against Growing and Non-growing Forms of B. burgdorferi. Frontiers in medicine, 7, 6. https://doi.org/10.3389/fmed.2020.00006
115. Goc, A., & Rath, M. (2016). The anti-borreliae efficacy of phytochemicals and micronutrients: an update. Therapeutic advances in infectious disease, 3(3-4), 75–82. https://doi.org/10.1177/2049936116655502
116. Hayashi, K., Kamiya, M., & Hayashi, T. (1995). Virucidal effects of the steam distillate from Houttuynia cordata and its components on HSV-1, influenza virus, and HIV. Planta medica, 61(3), 237–241. https://doi.org/10.1055/s-2006-958063
117. Kolb, B., Riesterer, L., Widenhorn, A. M., & Bier, L. (2020). Monitoring of Hydrogen Emission from Bacteria in Food, Animals and in the Blood of Humans Suffering from Lyme Disease by A Specific Hydrogen Sensor. Antibiotics (Basel, Switzerland), 9(7), 427. https://doi.org/10.3390/antibiotics9070427
118. Borjan, D., Leitgeb, M., Knez, Ž., & Hrnčič, M. K. (2020). Microbiological and Antioxidant Activity of Phenolic Compounds in Olive Leaf Extract. Molecules (Basel, Switzerland), 25(24), 5946. https://doi.org/10.3390/molecules25245946
119. Weiss J. (2018). Herb–Drug Interaction Potential of Anti-Borreliae Effective Extracts from Uncaria tomentosa (Samento) and Otoba parvifolia (Banderol) Assessed In Vitro. Molecules (Basel, Switzerland), 24(1), 137. https://doi.org/10.3390/molecules24010137

Inflammation

120. Zambrano, M. C., Beklemisheva, A. A., Bryksin, A. V., Newman, S. A., & Cabello, F. C. (2004). Borrelia burgdorferi binds to, invades, and colonizes native type I collagen lattices. Infection and immunity, 72(6), 3138–3146. https://doi.org/10.1128/IAI.72.6.3138-3146.2004
121. Le, N. T., Xue, M., Castelnoble, L. A., & Jackson, C. J. (2007). The dual personalities of matrix metalloproteinases in inflammation. Frontiers in bioscience : a journal and virtual library, 12, 1475–1487. https://doi.org/10.2741/2161
122. Ramesh, G., Didier, P. J., England, J. D., Santana-Gould, L., Doyle-Meyers, L. A., Martin, D. S., Jacobs, M. B., & Philipp, M. T. (2015). Inflammation in the pathogenesis of lyme neuroborreliosis. The American journal of pathology, 185(5), 1344–1360. https://doi.org/10.1016/j.ajpath.2015.01.024
123. Espinoza, J. L., Trung, L. Q., Inaoka, P. T., Yamada, K., An, D. T., Mizuno, S., Nakao, S., & Takami, A. (2017). The Repeated Administration of Resveratrol Has Measurable Effects on Circulating T-Cell Subsets in Humans. Oxidative medicine and cellular longevity, 2017, 6781872. https://doi.org/10.1155/2017/6781872
124. Dong, R., Zhang, M., Hu, Q., Zheng, S., Soh, A., Zheng, Y., & Yuan, H. (2018). Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review). International journal of molecular medicine, 41(2), 599–614. https://doi.org/10.3892/ijmm.2017.3311
125. Saltzman, E. T., Palacios, T., Thomsen, M., & Vitetta, L. (2018). Intestinal Microbiome Shifts, Dysbiosis, Inflammation, and Non-alcoholic Fatty Liver Disease. Frontiers in microbiology, 9, 61. https://doi.org/10.3389/fmicb.2018.00061

Inflammation

126. Wu, H. J., & Wu, E. (2012). The role of gut microbiota in immune homeostasis and autoimmunity. Gut microbes, 3(1), 4–14. https://doi.org/10.4161/gmic.19320
127. de Jong, P.R., González-Navajas, J.M. & Jansen, N.J.G. The digestive tract as the origin of systemic inflammation. Crit Care 20, 279 (2016). https://doi.org/10.1186/s13054-016-1458-3
128. Sandek, A., Bjarnason, I., Volk, H. D., Crane, R., Meddings, J. B., Niebauer, J., Kalra, P. R., Buhner, S., Herrmann, R., Springer, J., Doehner, W., von Haehling, S., Anker, S. D., & Rauchhaus, M. (2012). Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. International journal of cardiology, 157(1), 80–85. https://doi.org/10.1016/j.ijcard.2010.12.016
129. Hodges, R. E., & Minich, D. M. (2015). Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. Journal of nutrition and metabolism, 2015, 760689. https://doi.org/10.1155/2015/760689
130. Ma, Q., Xing, C., Long, W. et al. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. J Neuroinflammation 16, 53 (2019). https://doi.org/10.1186/s12974-019-1434-3

Galectin-3

131. Soares, L. C., Al-Dalahmah, O., Hillis, J., Young, C. C., Asbed, I., Sakaguchi, M., O'Neill, E., & Szele, F. G. (2021). Novel Galectin-3 Roles in Neurogenesis, Inflammation and Neurological Diseases. Cells, 10(11), 3047. https://doi.org/10.3390/cells10113047
132. Blanchard, H., Yu, X., Collins, P. M., & Bum-Erdene, K. (2014). Galectin-3 inhibitors: a patent review (2008-present). Expert opinion on therapeutic patents, 24(10), 1053–1065. https://doi.org/10.1517/13543776.2014.947961
133. Fermino, M. L., Polli, C. D., Toledo, K. A., Liu, F. T., Hsu, D. K., Roque-Barreira, M. C., Pereira-da-Silva, G., Bernardes, E. S., & Halbwachs-Mecarelli, L. (2011). LPS-induced galectin-3 oligomerization results in enhancement of neutrophil activation. PloS one, 6(10), e26004. https://doi.org/10.1371/journal.pone.0026004
134. Jawhara, S., Thuru, X., Standaert-Vitse, A., Jouault, T., Mordon, S., Sendid, B., Desreumaux, P., & Poulain, D. (2008). Colonization of mice by Candida albicans is promoted by chemically induced colitis and augments inflammatory responses through galectin-3. The Journal of infectious diseases, 197(7), 972–980. https://doi.org/10.1086/528990
135. Díaz-Alvarez, L., & Ortega, E. (2017). The Many Roles of Galectin-3, a Multifaceted Molecule, in Innate Immune Responses against Pathogens. Mediators of inflammation, 2017, 9247574. https://doi.org/10.1155/2017/9247574
136. Saltzman, E. T., Palacios, T., Thomsen, M., & Vitetta, L. (2018). Intestinal Microbiome Shifts, Dysbiosis, Inflammation, and Non-alcoholic Fatty Liver Disease. Frontiers in microbiology, 9, 61. https://doi.org/10.3389/fmicb.2018.00061
137. Croston TL, Lemons AR, Barnes MA, Goldsmith WT, Orandle MS, Nayak AP, Germolec DR, Green BJ, Beezhold DH. Inhalation of *Stachybotrys chartarum* Fragments Induces Pulmonary Arterial Remodeling. Am J Respir Cell Mol Biol. 2020 May;62(5):563-576.
138. Teirilä L, Karvala K, Ahonen N, Riska H, Pietinalho A, Tuominen P, Piirilä P, Puustinen A, Wolff H. Proteomic changes of alveolar lining fluid in illnesses associated with exposure to inhaled non-infectious microbial particles. PLoS One. 2014 Jul 17;9(7):e102624.

Galectin-3

137. Wolfert, M. A., & Boons, G. J. (2013). Adaptive immune activation: glycosylation does matter. Nature chemical biology, 9(12), 776–784. https://doi.org/10.1038/nchembio.1403
138. Xu, G. R., Zhang, C., Yang, H. X., Sun, J. H., Zhang, Y., Yao, T. T., Li, Y., Ruan, L., An, R., & Li, A. Y. (2020). Modified citrus pectin ameliorates myocardial fibrosis and inflammation via suppressing galectin-3 and TLR4/MyD88/NF-κB signaling pathway. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 126, 110071. https://doi.org/10.1016/j.biopha.2020.110071
139. Ma, Z., Han, Q., Wang, X., Ai, Z., & Zheng, Y. (2016). Galectin-3 Inhibition Is Associated with Neuropathic Pain Attenuation after Peripheral Nerve Injury. PloS one, 11(2), e0148792. https://doi.org/10.1371/journal.pone.0148792
140. Yong Hu, Mélissa Yéléhé-Okouma, Hang-Korng Ea, Jean-Yves Jouzeau, Pascal Reboul. Galectin3: A key player in arthritis. Joint Bone Spine, Elsevier Masson, 2017, 84 (1), pp.15-20. ff10.1016/j.jbspin.2016.02.029ff. Ffhal-01704704f
141. Fermino, M. L., Polli, C. D., Toledo, K. A., Liu, F. T., Hsu, D. K., Roque-Barreira, M. C., Pereira-da-Silva, G., Bernardes, E. S., & Halbwachs-Mecarelli, L. (2011). LPS-induced galectin-3 oligomerization results in enhancement of neutrophil activation. PloS one, 6(10), e26004. https://doi.org/10.1371/journal.pone.0026004
142. Ma, Z., Han, Q., Wang, X., Ai, Z., & Zheng, Y. (2016). Galectin-3 Inhibition Is Associated with Neuropathic Pain Attenuation after Peripheral Nerve Injury. PloS one, 11(2), e0148792. https://doi.org/10.1371/journal.pone.0148792

Galectin-3

143. Ramachandran, C., Wilk, B. J., Hotchkiss, A., Chau, H., Eliaz, I., & Melnick, S. J. (2011). Activation of human T-helper/inducer cell, T-cytotoxic cell, B-cell, and natural killer (NK)-cells and induction of natural killer cell activity against K562 chronic myeloid leukemia cells with modified citrus pectin. BMC complementary and alternative medicine, 11, 59. https://doi.org/10.1186/1472-6882-11-59
144. Zhao, Z. Y., Liang, L., Fan, X., Yu, Z., Hotchkiss, A. T., Wilk, B. J., & Eliaz, I. (2008). The role of modified citrus pectin as an effective chelator of lead in children hospitalized with toxic lead levels. Alternative therapies in health and medicine, 14(4), 34–38.
145. Eliaz, I., Weil, E., & Wilk, B. (2007). Integrative medicine and the role of modified citrus pectin/alginates in heavy metal chelation and detoxification--five case reports. Forschende Komplementarmedizin (2006), 14(6), 358–364. https://doi.org/10.1159/000109829
146. Eliaz, I., Hotchkiss, A. T., Fishman, M. L., & Rode, D. (2006). The effect of modified citrus pectin on urinary excretion of toxic elements. Phytotherapy research : PTR, 20(10), 859–864. https://doi.org/10.1002/ptr.1953
147. Feng, J., Leone, J., Schweig, S., & Zhang, Y. (2020). Evaluation of Natural and Botanical Medicines for Activity Against Growing and Non-growing Forms of B. burgdorferi. Frontiers in medicine, 7, 6. https://doi.org/10.3389/fmed.2020.00006

Babesia

148. Jalovecka, M., Sojka, D., Ascencio, M., & Schnittger, L. (2019). Babesia Life Cycle - When Phylogeny Meets Biology. Trends in parasitology, 35(5), 356–368. https://doi.org/10.1016/j.pt.2019.01.007
149. Woolley, A. E., Montgomery, M. W., Savage, W. J., Achebe, M. O., Dunford, K., Villeda, S., Maguire, J. H., & Marty, F. M. (2017). Post-Babesiosis Warm Autoimmune Hemolytic Anemia. The New England journal of medicine, 376(10), 939–946. https://doi.org/10.1056/NEJMoa1612165
150. Lobo, C. A., Rodriguez, M., & Cursino-Santos, J. R. (2012). Babesia and red cell invasion. Current opinion in hematology, 19(3), 170–175. https://doi.org/10.1097/MOH.0b013e3283522245a
151. Wright, I. G., Goodger, B. V., Buffington, G. D., Clark, I. A., Parrodi, F., & Waltisbuhl, D. J. (1989). Immunopathophysiology of babesial infections. Transactions of the Royal Society of Tropical Medicine and Hygiene, 83 Suppl, 11–13. https://doi.org/10.1016/0035-9203(89)90596-8
152. Djokic, V., Akoolo, L., & Parveen, N. (2018). Babesia microti Infection Changes Host Spleen Architecture and Is Cleared by a Th1 Immune Response. Frontiers in microbiology, 9, 85. https://doi.org/10.3389/fmicb.2018.00085
153. Xiping, Z., Chuyang, L., Jie, Z., Yuefang, R., & Meili, M. (2009). Protection of Salvia miltiorrhizae to the spleen and thymus of rats with severe acute pancreatitis or obstructive jaundice. Mediators of inflammation, 2009, 186136. https://doi.org/10.1155/2009/186136

Babesia

154. Nassar, Y., & Richter, S. (2017). Babesiosis Presenting as Acute Liver Failure. Case reports in gastroenterology, 11(3), 769–773. https://doi.org/10.1159/000485373
155. Djokic, V., Rocha, S. C., & Parveen, N. (2021). Lessons Learned for Pathogenesis, Immunology, and Disease of Erythrocytic Parasites: Plasmodium and Babesia. Frontiers in cellular and infection microbiology, 11, 685239. https://doi.org/10.3389/fcimb.2021.685239
156. Aguilar-Delfin, I., Wettstein, P. J., & Persing, D. H. (2003). Resistance to acute babesiosis is associated with interleukin-12- and gamma interferon-mediated responses and requires macrophages and natural killer cells. Infection and immunity, 71(4), 2002–2008. https://doi.org/10.1128/IAI.71.4.2002-2008.2003
157. Böger R. H. (2014). The pharmacodynamics of L-arginine. Alternative therapies in health and medicine, 20(3), 48–54.
158. Lee, E., Son, J. E., Byun, S., Lee, S. J., Kim, Y. A., Liu, K., Kim, J., Lim, S. S., Park, J. H., Dong, Z., Lee, K. W., & Lee, H. J. (2013). CDK2 and mTOR are direct molecular targets of isoangustone A in the suppression of human prostate cancer cell growth. Toxicology and applied pharmacology, 272(1), 12–20. https://doi.org/10.1016/j.taap.2013.04.030
159. Gray, K. A., Gresty, K. J., Chen, N., Zhang, V., Gutteridge, C. E., Peatey, C. L., Chavchich, M., Waters, N. C., & Cheng, Q. (2016). Correlation between Cyclin Dependent Kinases and Artemisinin-Induced Dormancy in Plasmodium falciparum In Vitro. PloS one, 11(6), e0157906. https://doi.org/10.1371/journal.pone.0157906

Babesia

160. Hsu, S. L., Hsieh, Y. C., Hsieh, W. C., & Chou, C. J. (2001). Baicalein induces a dual growth arrest by modulating multiple cell cycle regulatory molecules. European journal of pharmacology, 425(3), 165–171. https://doi.org/10.1016/s0014-2999(01)01144-x
161. Lin, C. B., Lin, C. C., & Tsay, G. J. (2012). 6-Gingerol Inhibits Growth of Colon Cancer Cell LoVo via Induction of G2/M Arrest. Evidence-based complementary and alternative medicine : eCAM, 2012, 326096. https://doi.org/10.1155/2012/326096
162. Li, Y., Liang, F., Jiang, W., Yu, F., Cao, R., Ma, Q., Dai, X., Jiang, J., Wang, Y., & Si, S. (2007). DH334, a beta-carboline anti-cancer drug, inhibits the CDK activity of budding yeast. Cancer biology & therapy, 6(8), 1193–1199.
163. Lee, B., Kim, C. H., & Moon, S. K. (2006). Honokiol causes the p21WAF1-mediated G(1)-phase arrest of the cell cycle through inducing p38 mitogen activated protein kinase in vascular smooth muscle cells. FEBS letters, 580(22), 5177–5184. https://doi.org/10.1016/j.febslet.2006.08.064
164. Sheu, M. J., Huang, G. J., Wu, C. H., Chen, J. S., Chang, H. Y., Chang, S. J., & Chung, J. G. (2008). Ethanol extract of Dunaliella salina induces cell cycle arrest and apoptosis in A549 human non-small cell lung cancer cells. In vivo (Athens, Greece), 22(3), 369–378.
165. Chauvin, A., Moreau, E., Bonnet, S., Plantard, O., & Malandrin, L. (2009). Babesia and its hosts: adaptation to long-lasting interactions as a way to achieve efficient transmission. Veterinary research, 40(2), 37. https://doi.org/10.1051/vetres/2009020

Babesia

166. Ho, J., Carey, E., Carey, D. E., & Krause, P. J. (2021). Recurrence of Human Babesiosis Caused by Reinfection. Emerging infectious diseases, 27(10), 2658–2661. https://doi.org/10.3201/eid2710.211240
167. Li, Y., Terkawi, M. A., Nishikawa, Y., Aboge, G. O., Luo, Y., Ooka, H., Goo, Y. K., Yu, L., Cao, S., Sun, Y., Yamagishi, J., Masatani, T., Yokoyama, N., Igarashi, I., & Xuan, X. (2012). Macrophages are critical for cross-protective immunity conferred by Babesia microti against Babesia rodhaini infection in mice. Infection and immunity, 80(1), 311–320. https://doi.org/10.1128/IAI.05900-11
168. Jang, S. I., Jeong, S. I., Kim, K. J., Kim, H. J., Yu, H. H., Park, R., Kim, H. M., & You, Y. O. (2003). Tanshinone IIA from Salvia miltiorrhiza inhibits inducible nitric oxide synthase expression and production of TNF-alpha, IL-1beta and IL-6 in activated RAW 264.7 cells. Planta medica, 69(11), 1057–1059. https://doi.org/10.1055/s-2003-45157
169. Kimura, Y., & Okuda, H. (2001). Resveratrol isolated from Polygonum cuspidatum root prevents tumor growth and metastasis to lung and tumor-induced neovascularization in Lewis lung carcinoma-bearing mice. The Journal of nutrition, 131(6), 1844–1849. https://doi.org/10.1093/jn/131.6.1844
170. Wang, Y., Wang, Y., You, F., & Xue, J. (2020). Novel use for old drugs: The emerging role of artemisinin and its derivatives in fibrosis. Pharmacological research, 157, 104829. https://doi.org/10.1016/j.phrs.2020.104829
171. Wu, C., Kan, H., Hu, M., Liu, X., Boye, A., Jiang, Y., Wu, J., Wang, J., Yang, X., & Yang, Y. (2018). Compound Astragalus and Salvia miltiorrhiza extract inhibits hepatocarcinogenesis via modulating TGF-β/TβR and Imp7/8. Experimental and therapeutic medicine, 16(2), 1052–1060. https://doi.org/10.3892/etm.2018.6292

Babesia

172. Wu, Z., Jia, M., Zhao, W., Huang, X., Yang, X., Chen, D., Qiaolongbatu, X., Li, X., Wu, J., Qian, F., Lou, Y., & Fan, G. (2022). Schisandrol A, the main active ingredient of Schisandrae Chinensis Fructus, inhibits pulmonary fibrosis through suppression of the TGF-β signaling pathway as revealed by UPLC-Q-TOF/MS, network pharmacology and experimental verification. Journal of ethnopharmacology, 289, 115031. Advance online publication. https://doi.org/10.1016/j.jep.2022.115031
173. Bokhari, A. A., & Syed, V. (2015). Inhibition of Transforming Growth Factor-β (TGF-β) Signaling by Scutellaria baicalensis and Fritillaria cirrhosa Extracts in Endometrial Cancer. Journal of cellular biochemistry, 116(8), 1797–1805. https://doi.org/10.1002/jcb.25138
174. Yu, X., Su, Q., Geng, J., Liu, H., Liu, Y., Liu, J., Shi, Y., & Zou, Y. (2021). Ginkgo biloba leaf extract prevents diabetic nephropathy through the suppression of tissue transglutaminase. Experimental and therapeutic medicine, 21(4), 333. https://doi.org/10.3892/etm.2021.9764
175. Kim, S. C., Kang, J. I., Hyun, J. W., Kang, J. H., Koh, Y. S., Kim, Y. H., Kim, K. H., Ko, J. H., Yoo, E. S., & Kang, H. K. (2017). 4-O-Methylhonokiol Protects HaCaT Cells from TGF-β1-Induced Cell Cycle Arrest by Regulating Canonical and Non-Canonical Pathways of TGF-β Signaling. Biomolecules & therapeutics, 25(4), 417–426. https://doi.org/10.4062/biomolther.2016.003
176. Zeng, J., Dou, Y., Guo, J., Wu, X., & Dai, Y. (2013). Paeoniflorin of Paeonia lactiflora prevents renal interstitial fibrosis induced by unilateral ureteral obstruction in mice. Phytomedicine : international journal of phytotherapy and phytopharmacology, 20(8-9), 753–759. https://doi.org/10.1016/j.phymed.2013.02.010

Babesia

177. Dong, J., & Ma, Q. (2018). Type 2 Immune Mechanisms in Carbon Nanotube-Induced Lung Fibrosis. Frontiers in immunology, 9, 1120. https://doi.org/10.3389/fimmu.2018.01120
178. Endo, M., Oyadomari, S., Terasaki, Y., Takeya, M., Suga, M., Mori, M., & Gotoh, T. (2003). Induction of arginase I and II in bleomycin-induced fibrosis of mouse lung. American journal of physiology. Lung cellular and molecular physiology, 285(2), L313–L321. https://doi.org/10.1152/ajplung.00434.2002
179. Aguilar-Delfin, I., Wettstein, P. J., & Persing, D. H. (2003). Resistance to acute babesiosis is associated with interleukin-12- and gamma interferon-mediated responses and requires macrophages and natural killer cells. Infection and immunity, 71(4), 2002–2008. https://doi.org/10.1128/IAI.71.4.2002-2008.2003
180. Stich, R. W., Shoda, L. K., Dreewes, M., Adler, B., Jungi, T. W., & Brown, W. C. (1998). Stimulation of nitric oxide production in macrophages by Babesia bovis. Infection and immunity, 66(9), 4130–4136. https://doi.org/10.1128/IAI.66.9.4130-4136.1998
181. Clawson, M. L., Paciorkowski, N., Rajan, T. V., La Vake, C., Pope, C., La Vake, M., Wikel, S. K., Krause, P. J., & Radolf, J. D. (2002). Cellular immunity, but not gamma interferon, is essential for resolution of Babesia microti infection in BALB/c mice. Infection and immunity, 70(9), 5304–5306. https://doi.org/10.1128/IAI.70.9.5304-5306.2002
182. Skariah, S., Arnaboldi, P., Dattwyler, R. J., Sultan, A. A., Gaylets, C., Walwyn, O., Mulhall, H., Wu, X., Dargham, S. R., & Mordue, D. G. (2017). Elimination of Babesia microti Is Dependent on Intraerythrocytic Killing and CD4+ T Cells. Journal of immunology (Baltimore, Md. : 1950), 199(2), 633–642. https://doi.org/10.4049/jimmunol.1601193

Babesia

183. Khan, M. A., Ahmed, R. S., Chandra, N., Arora, V. K., & Ali, A. (2019). In vivo, Extract from Withania somnifera Root Ameliorates Arthritis via Regulation of Key Immune Mediators of Inflammation in Experimental Model of Arthritis. Anti-inflammatory & anti-allergy agents in medicinal chemistry, 18(1), 55–70. https://doi.org/10.2174/1871523017666181116092934
184. Soo-Jeung Park, S. Park, Minhee Lee, M. Lee, Jeong-Moon Yun, J. Yun, Dakyung Kim, D. Kim, Dong Hwan Oh, D. Hwan Oh, Jinkyung Kim, J. Kim, Myeongkuk Shim, M. Shim, Hee-Jin Oh, H. Oh, & Jeongmin Lee, J. Lee. (2021). Deer Velvet and Eleutherococcus senticosus Mixture Regulated Immune Function in C57BL/6N Mice with Immunosuppression Induced by Forced Swimming. Journal of medicinal food, 24, 1213-1221. doi: 10.1089/jmf.2021.K.0060
185. Liu, Q. Y., & Yao, Y. M. (2011). Zhonghua shao shang za zhi = Zhonghua shaoshang zazhi = Chinese journal of burns, 27(2), 95–99.
186. Buhner, SH. (2015). Natural Treatments for Lyme Coinfections: Anaplasma, Babesia, and Ehrlichia. Inner Traditions Bear and Company.
187. Zhang, Y., Alvarez-Manzo, H., Leone, J., Schweig, S., & Zhang, Y. (2021). Botanical Medicines Cryptolepis sanguinolenta, Artemisia annua, Scutellaria baicalensis, Polygonum cuspidatum, and Alchornea cordifolia Demonstrate Inhibitory Activity Against Babesia duncani. Frontiers in cellular and infection microbiology, 11, 624745. https://doi.org/10.3389/fcimb.2021.624745

Babesia

188. Chumpol, W, et al. (2018). The Antibacterial Activity of the Aqueous Extract of Sida Acuta Burm. F. Southeast Asian J Trop Med Public Health, Vol 49(2), 285-291.
189. Geissberger, P., & Séquin, U. (1991). Constituents of Bidens pilosa L.: do the components found so far explain the use of this plant in traditional medicine?. Acta tropica, 48(4), 251–261. https://doi.org/10.1016/0001-706x(91)90013-a
190. Elkady, A. I., Abuzinadah, O. A., Baeshen, N. A., & Rahmy, T. R. (2012). Differential control of growth, apoptotic activity, and gene expression in human breast cancer cells by extracts derived from medicinal herbs Zingiber officinale. Journal of biomedicine & biotechnology, 2012, 614356. https://doi.org/10.1155/2012/614356
191. Guo, H. M., Sun, Y. M., Zhang, S. X., Ju, X. L., Xie, A. Y., Li, J., Zou, L., Sun, X. D., Li, H. L., & Zheng, Y. (2015). Metabolism and pharmacokinetics of 8-hydroxypiperidinylmethyl-baicalein (BA-j) as a novel selective CDK1 inhibitor in monkey. Fitoterapia, 107, 36–43. https://doi.org/10.1016/j.fitote.2015.10.001
192. Goda, M. S., Nafie, M. S., Awad, B. M., Abdel-Kader, M. S., Ibrahim, A. K., Badr, J. M., & Eltamany, E. E. (2021). In Vitro and In Vivo Studies of Anti-Lung Cancer Activity of Artemesia judaica L. Crude Extract Combined with LC-MS/MS Metabolic Profiling, Docking Simulation and HPLC-DAD Quantification. Antioxidants (Basel, Switzerland), 11(1), 17. https://doi.org/10.3390/antiox11010017

Babesia

194. Lee, B. C., Doo, H. K., Lee, H. J., Jin, S. Y., Jung, J. H., Hong, S. J., Lee, S. H., Kim, S. D., Park, J. K., Leem, K. H., & Ahn, S. Y. (2004). The inhibitory effects of aqueous extract of Magnolia officinalis on human mesangial cell proliferation by regulation of platelet-derived growth factor-BB and transforming growth factor-beta1 expression. Journal of pharmacological sciences, 94(1), 81–85. https://doi.org/10.1254/jphs.94.81
195. Lee, Y. M., Lim, D. Y., Choi, H. J., Jung, J. I., Chung, W. Y., & Park, J. H. (2009). Induction of cell cycle arrest in prostate cancer cells by the dietary compound isoliquiritigenin. Journal of medicinal food, 12(1), 8–14. https://doi.org/10.1089/jmf.2008.0039
196. Ugwuezumba, P & Nwankpa, P & Emengaha, F & Ekweogu, C & Chukwuemeka, O & Etteh, Chinedu & Godfrey, Obinna. (2018). Alteration of Haematological Indices on Administration of Ethanol Leaf and Root Extracts of Sida Acuta in Albino Wistar Rats. Asian Journal of Science and Technology, 9(5), 8156-8159.
197. Böger R. H. (2014). The pharmacodynamics of L-arginine. Alternative therapies in health and medicine, 20(3), 48–54.
198. Jang, S. I., Jeong, S. I., Kim, K. J., Kim, H. J., Yu, H. H., Park, R., Kim, H. M., & You, Y. O. (2003). Tanshinone IIA from Salvia miltiorrhiza inhibits inducible nitric oxide synthase expression and production of TNF-alpha, IL-1beta and IL-6 in activated RAW 264.7 cells. Planta medica, 69(11), 1057–1059. https://doi.org/10.1055/s-2003-45157

Babesia

199. Wu, L. W., Chiang, Y. M., Chuang, H. C., Lo, C. P., Yang, K. Y., Wang, S. Y., & Shyur, L. F. (2007). A novel polyacetylene significantly inhibits angiogenesis and promotes apoptosis in human endothelial cells through activation of the CDK inhibitors and caspase-7. Planta medica, 73(7), 655–661. https://doi.org/10.1055/s-2007-981527
200. Jung, I., Kim, H., Moon, S., Lee, H., & Kim, B. (2020). Overview of Salvia miltiorrhiza as a Potential Therapeutic Agent for Various Diseases: An Update on Efficacy and Mechanisms of Action. Antioxidants (Basel, Switzerland), 9(9), 857. https://doi.org/10.3390/antiox9090857
201. Hogan, F. S., Krishnegowda, N. K., Mikhailova, M., & Kahlenberg, M. S. (2007). Flavonoid, silibinin, inhibits proliferation and promotes cell-cycle arrest of human colon cancer. The Journal of surgical research, 143(1), 58–65. https://doi.org/10.1016/j.jss.2007.03.080
202. Luo, J., Liu, M., Wu, X., Dou, Y., Xia, Y., Dai, Y., & Wei, Z. (2015). DGAEE, a newly synthesized derivative of glycyrrhetinic acid, potently attenuates mouse septic shock via its main metabolite DGA in an IL-10-dependent manner. International immunopharmacology, 29(2), 583–590. https://doi.org/10.1016/j.intimp.2015.09.025
203. Wilasrusmee, C., Kittur, S., Shah, G., Siddiqui, J., Bruch, D., Wilasrusmee, S., & Kittur, D. S. (2002). Immunostimulatory effect of Silybum Marianum (milk thistle) extract. Medical science monitor : international medical journal of experimental and clinical research, 8(11), BR439–BR443.

Babesia

204. Al-Ghezi, Z. Z., Busbee, P. B., Alghetaa, H., Nagarkatti, P. S., & Nagarkatti, M. (2019). Combination of cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), mitigates experimental autoimmune encephalomyelitis (EAE) by altering the gut microbiome. Brain, behavior, and immunity, 82, 25–35. https://doi.org/10.1016/j.bbi.2019.07.028

205. Bao, X., Li, L., & Xue, X. (2019). Flavonoids from Scutellaria barbata inhibit activation of tumor-associated macrophages by blocking the Toll-like receptor 4/myeloid differentiation factor 88/nuclear factor-κB signaling pathway. Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan, 39(2), 160–165.

206. Kim, J. H., Shin, C. Y., Jang, S. W., Kim, D. S., Lee, W., Kim, H. G., & Kim, H. R. (2021). Anti-inflammatory effects of DA-9601, an extract of Artemisia asiatica, on aceclofenac-induced acute enteritis. The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology, 25(5), 439–448. https://doi.org/10.4196/kjpp.2021.25.5.439

207. Saggam, A., Limgaokar, K., Borse, S., Chavan-Gautam, P., Dixit, S., Tillu, G., & Patwardhan, B. (2021). Withania somnifera (L.) Dunal: Opportunity for Clinical Repurposing in COVID-19 Management. Frontiers in pharmacology, 12, 623795. https://doi.org/10.3389/fphar.2021.623795

208. Cui, Y., Wang, Q., Sun, R., Guo, L., Wang, M., Jia, J., Xu, C., & Wu, R. (2018). Astragalus membranaceus (Fisch.) Bunge repairs intestinal mucosal injury induced by LPS in mice. BMC complementary and alternative medicine, 18(1), 230. https://doi.org/10.1186/s12906-018-2298-2

Babesia

209. Richard S. A. (2021). Exploring the Pivotal Immunomodulatory and Anti-Inflammatory Potentials of Glycyrrhizic and Glycyrrhetinic Acids. Mediators of inflammation, 2021, 6699560. https://doi.org/10.1155/2021/6699560

210. Jung, E. J., Paramanantham, A., Kim, H. J., Shin, S. C., Kim, G. S., Jung, J. M., Hong, S. C., Chung, K. H., Kim, C. W., & Lee, W. S. (2022). Identification of Growth Factors, Cytokines and Mediators Regulated by Artemisia annua L. Polyphenols (pKAL) in HCT116 Colorectal Cancer Cells: TGF-β1 and NGF-β Attenuate pKAL-Induced Anticancer Effects via NF-κB p65 Upregulation. International journal of molecular sciences, 23(3), 1598. https://doi.org/10.3390/ijms23031598

211. Wei, Y., Wu, Y., Feng, K., Zhao, Y., Tao, R., Xu, H., & Tang, Y. (2020). Astragaloside IV inhibits cardiac fibrosis via miR-135a-TRPM7-TGF-β/Smads pathway. Journal of ethnopharmacology, 249, 112404. https://doi.org/10.1016/j.jep.2019.112404

212. Chen, Q., Zhang, H., Cao, Y., Li, Y., Sun, S., Zhang, J., & Zhang, G. (2017). Schisandrin B attenuates CCl4-induced liver fibrosis in rats by regulation of Nrf2-ARE and TGF-β/Smad signaling pathways. Drug design, development and therapy, 11, 2179–2191. https://doi.org/10.2147/DDDT.S137507

213. Wu, C., Kan, H., Hu, M., Liu, X., Boye, A., Jiang, Y., Wu, J., Wang, J., Yang, X., & Yang, Y. (2018). Compound Astragalus and Salvia miltiorrhiza extract inhibits hepatocarcinogenesis via modulating TGF-β/TβR and Imp7/8. Experimental and therapeutic medicine, 16(2), 1052–1060. https://doi.org/10.3892/etm.2018.6292

Babesia

214. Bokhari, A. A., & Syed, V. (2015). Inhibition of Transforming Growth Factor-β (TGF-β) Signaling by Scutellaria baicalensis and Fritillaria cirrhosa Extracts in Endometrial Cancer. Journal of cellular biochemistry, 116(8), 1797–1805. https://doi.org/10.1002/jcb.25138
215. Shin, W., Yoon, J., Oh, G. T., & Ryoo, S. (2013). Korean red ginseng inhibits arginase and contributes to endotheliumdependent vasorelaxation through endothelial nitric oxide synthase coupling. Journal of ginseng research, 37(1), 64–73. https://doi.org/10.5142/jgr.2013.37.64
216. Kim, S. W., Cuong, T. D., Hung, T. M., Ryoo, S., Lee, J. H., & Min, B. S. (2013). Arginase II inhibitory activity of flavonoid compounds from Scutellaria indica. Archives of pharmacal research, 36(8), 922–926. https://doi.org/10.1007/s12272-013-0125-3
217. dos Reis, M. B., Manjolin, L. C., Maquiaveli, C., Santos-Filho, O. A., & da Silva, E. R. (2013). Inhibition of Leishmania (Leishmania) amazonensis and rat arginases by green tea EGCG, (+)-catechin and (-)-epicatechin: a comparative structural analysis of enzyme-inhibitor interactions. PloS one, 8(11), e78387. https://doi.org/10.1371/journal.pone.0078387
218. Shin, W., Yoon, J., Oh, G. T., & Ryoo, S. (2013). Korean red ginseng inhibits arginase and contributes to endotheliumdependent vasorelaxation through endothelial nitric oxide synthase coupling. Journal of ginseng research, 37(1), 64–73. https://doi.org/10.5142/jgr.2013.37.64

Babesia

219. Lu, J., Chen, X., Zhang, Y., Xu, J., Zhang, L., Li, Z., Liu, W., Ouyang, J., Han, S., & He, X. (2013). Astragalus polysaccharide induces anti-inflammatory effects dependent on AMPK activity in palmitate-treated RAW264.7 cells. International journal of molecular medicine, 31(6), 1463–1470. https://doi.org/10.3892/ijmm.2013.1335
220. Abdelkawy KS, Elbarbry F. (2017). (–)-Epictaechin; A Plant Arginase Inhibitor with Favorable Pharmacokinetic Profile. Ann Clin Exp Hypertension 5(1): 1044.
221. Bani, S., Gautam, M., Sheikh, F. A., Khan, B., Satti, N. K., Suri, K. A., Qazi, G. N., & Patwardhan, B. (2006). Selective Th1 up-regulating activity of Withania somnifera aqueous extract in an experimental system using flow cytometry. Journal of ethnopharmacology, 107(1), 107–115. https://doi.org/10.1016/j.jep.2006.02.016
222. Zhang, Y., Alvarez-Manzo, H., Leone, J., Schweig, S., & Zhang, Y. (2021). Botanical Medicines Cryptolepis sanguinolenta, Artemisia annua, Scutellaria baicalensis, Polygonum cuspidatum, and Alchornea cordifolia Demonstrate Inhibitory Activity Against Babesia duncani. Frontiers in cellular and infection microbiology, 11, 624745. https://doi.org/10.3389/fcimb.2021.624745

Addendum

- *Epsom Salt Detox: Benefits and How It Works*. 26 Apr. 2018, https://www.medicalnewstoday.com/articles/321627.
- Hussain, Joy, and Marc Cohen. "Clinical Effects of Regular Dry Sauna Bathing: A Systematic Review." *Evidence-Based Complementary and Alternative Medicine*, vol. 2018, 2018, pp. 1–30. *DOI.org (Crossref)*, https://doi.org/10.1155/2018/1857413.
- Jasion VS, Burnett BP. Survival and Digestibility of Orally Administered Immunoglobulin Preparations Containing IgG Through the Gastrointestinal Tract in Humans. Nutrition Journal 2015;14:22 DOI 10.1186/s12937-015- 0010-7. 3.
- Petschow BW, Burnett B, Shaw AL, Weaver EM, Klein GL. Serum-derived bovine immunoglobulin/protein isolate: postulated mechanism of action for management of enteropathy, Clin Exp Gastroenterology. 2014;7:181- 190
- Uraz, Suleyman, et al. "N-Acetylcysteine Expresses Powerful Anti-Inflammatory and Antioxidant Activities Resulting in Complete Improvement of Acetic Acid-Induced Colitis in Rats." *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 73, no. 1, Feb. 2013, pp. 61–66. *DOI.org (Crossref)*, https://doi.org/10.3109/00365513.2012.734859.
- Khoshbaten M, Aliasgarzadeh A, Masnadi K, Tarzamani MK, Farhang S, Babaei H, Kiani J, Zaare M, Najafipoor F. N-acetylcysteine improves liver function in patients with non-alcoholic Fatty liver disease. Hepat Mon. 2010 Winter;10(1):12-6. Epub 2010 Mar 1. PMID: 22308119; PMCID: PMC3270338.
- Horowitz, Richard. *Why Can't I Get Better? Solving the Mystery of Lyme and Chronic Disease*. St. Martin's, 2013.
- Rabbani, G. H., et al. "Green Banana and Pectin Improve Small Intestinal Permeability and Reduce Fluid Loss in Bangladeshi Children with Persistent Diarrhea." *Digestive Diseases and Sciences*, vol. 49, no. 3, Mar. 2004, pp. 475–84. *DOI.org (Crossref)*, https://doi.org/10.1023/B:DDAS.0000020507.25910.cf.

Addendum

- Suzuki, Takuya. “Regulation of the Intestinal Barrier by Nutrients: The Role of Tight Junctions.” *Animal Science Journal*, vol. 91, no. 1, Jan. 2020, p. e13357. *DOI.org (Crossref)*, https://doi.org/10.1111/asj.13357.
- Zhang, Lichao, et al. “Effects of Berberine on the Gastrointestinal Microbiota.” *Frontiers in Cellular and Infection Microbiology*, vol. 10, Feb. 2021, p. 588517. *DOI.org (Crossref)*, https://doi.org/10.3389/fcimb.2020.588517.
- Heggers, John P., et al. “The Effectiveness of Processed Grapefruit-Seed Extract as An Antibacterial Agent: II. Mechanism of Action and *In Vitro* Toxicity.” *The Journal of Alternative and Complementary Medicine*, vol. 8, no. 3, June 2002, pp. 333–40. *DOI.org (Crossref)*, https://doi.org/10.1089/107555302760128023.
- Pérez-Torres, Israel, et al. “Beneficial Effects of the Amino Acid Glycine.” *Mini-Reviews in Medicinal Chemistry*, vol. 17, no. 1, Nov. 2016, pp. 15–32. *DOI.org (Crossref)*, https://doi.org/10.2174/1389557516666160609081602.
- Houghton, Christine A., et al. “Sulforaphane and Other Nutrigenomic Nrf2 Activators: Can the Clinician’s Expectation Be Matched by the Reality?” *Oxidative Medicine and Cellular Longevity*, vol. 2016, 2016, pp. 1–17. *DOI.org (Crossref)*, https://doi.org/10.1155/2016/7857186.
- Minich, Deanna M., and Benjamin I. Brown. “A Review of Dietary (Phyto)Nutrients for Glutathione Support.” *Nutrients*, vol. 11, no. 9, Sept. 2019, p. 2073. *PubMed Central*, https://doi.org/10.3390/nu11092073.
- Łoboś, Paulina, and Bożena Regulska-Ilow. “Link between Methyl Nutrients and the DNA Methylation Process in the Course of Selected Diseases in Adults.” *Roczniki Państwowego Zakładu Higieny*, 2021, pp. 123–36. *DOI.org (Crossref)*, https://doi.org/10.32394/rpzh.2021.0157.
- Jacob, Claus, et al. “Sulfur and Selenium: The Role of Oxidation State in Protein Structure and Function.” *Angewandte Chemie International Edition*, vol. 42, no. 39, Oct. 2003, pp. 4742–58. *DOI.org (Crossref)*, https://doi.org/10.1002/anie.200300573.

Addendum

- Watson, Bill. “What Is Acetylation And How Does It Help Detoxify Your Body?” *Xcode Life*, 11 Aug. 2021, https://www.xcode.life/genes-and-detox/what-is-acetylation-and-how-does-it-help-detoxify-your-body/
- Novkovic, Biljana. “Glucuronidation: Detox, Balance Hormones, & Genes.” *SelfDecode Health*, 13 Dec. 2019, https://health.selfdecode.com/blog/glucuronidation-detox-estrogen-hormone-balance-prevent-cancer-red-meat/.
- Maruti, Sonia S., et al. “Dietary and Demographic Correlates of Serum β-Glucuronidase Activity.” *Nutrition and Cancer*, vol. 62, no. 2, Jan. 2010, pp. 208–19. *DOI.org (Crossref)*, https://doi.org/10.1080/01635580903305375.
- Altern Med Rev. 2002 Aug;7(4):336-9. PMID: 12197785.
- Watts, Todd. “9 Old-School Toxin Binders (Plus, Meet a Better Binder).” *CellCore Biosciences*, https://cellcore.com/blogs/articles/9-old-school-toxin-binders-plus-meet-a-better-binder. Accessed 16 Dec. 2023.
- Schaumberger, Simone, et al. “Evaluation of the Endotoxin Binding Efficiency of Clay Minerals Using the Limulus Amebocyte Lysate Test: An in Vitro Study.” *AMB Express*, vol. 4, no. 1, 2014, p. 1. *DOI.org (Crossref)*, https://doi.org/10.1186/2191-0855-4-1.
- Eliaz I, Weil E, Schwarzbach J, Wilk B. Modified Citrus Pectin / Alginate Dietary Supplement Increased Fecal Excretion of Uranium: A Family. Altern Ther Health Med. 2019 Jul;25(4):20-24. PMID: 31202207.
- Zhao ZY, Liang L, Fan X, Yu Z, Hotchkiss AT, Wilk BJ, Eliaz I. The role of modified citrus pectin as an effective chelator of lead in children hospitalized with toxic lead levels. Altern Ther Health Med. 2008 Jul-Aug;14(4):34-8. Erratum in: Altern Ther Health Med. 2008 Nov-Dec;14(6):18. PMID: 18616067.
- Nakano S, Takekoshi H, Nakano M. Chlorella (Chlorella pyrenoidosa) supplementation decreases dioxin and increases immunoglobulin a concentrations in breast milk. J Med Food. 2007 Mar;10(1):134-42. doi: 10.1089/jmf.2006.023. PMID: 17472477.

Addendum

- Lamm, S., et al. “Persistent Response to Pneumococcal Vaccine in Individuals Supplemented with a Novel Water Soluble Extract of Uncaria Tomentosa, C-Med-100.” *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, vol. 8, no. 4, July 2001, pp. 267–74. *PubMed*, https://doi.org/10.1078/0944-7113-00046.
- Zhai, Zili, et al. “Enhancement of Innate and Adaptive Immune Functions by Multiple *Echinacea* Species.” *Journal of Medicinal Food*, vol. 10, no. 3, Sept. 2007, pp. 423–34. *DOI.org (Crossref)*, https://doi.org/10.1089/jmf.2006.257.
- Díaz-Alvarez L, Ortega E. The Many Roles of Galectin-3, a Multifaceted Molecule, in Innate Immune Responses against Pathogens. Mediators Inflamm. 2017;2017:9247574.
- Wolfert MA, Boons GJ. Adaptive immune activation: glycosylation does matter. Nat Chem Biol. 2013 Dec;9(12):776-84.
- Verhaegh, Dennis, et al. “The Role of Host Immune Cells and Borrelia Burgdorferi Antigens in the Etiology of Lyme Disease.” *European Cytokine Network*, vol. 28, no. 2, June 2017, pp. 70–84., https://doi.org/10.1684/ecn.2017.0396.
- Branda, J. A., & Strle, F. (2018). Advances in Serodiagnostic Testing for Lyme Disease Are at Hand. Clinical Infectious Diseases, 66(7), 1131-1132.
- Marques, A. R. (2008). Lyme Disease: A Review. Current Allergy and Asthma Reports, 8(4), 291-296.
- Pritt, B. S., Mead, P. S., Johnson, D. K. H., Howerth, E. W., & Sloan, L. M. (2016). Identification of a novel pathogenic Borrelia species causing Lyme borreliosis with unusually high spirochaetaemia: a descriptive study. The Lancet Infectious Diseases, 16(5), 556-564.
- Steere, A. C., Malawista, S. E., Snydman, D. R., Shope, R. E., Andiman, W. A., Ross, M. R., ... & Steele, F. M. (1977). Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis & Rheumatism, 20(1), 7-17.

Addendum

- Wormser, G. P., Nadelman, R. B., Dattwyler, R. J., Dennis, D. T., Shapiro, E. D., Steere, A. C., ... & Fish, D. (2006). Practice Guidelines for the Treatment of Lyme Disease. Clinical Infectious Diseases, 43(9), 1089-1134.
- Centers for Disease Control and Prevention (CDC). (2022). Lyme Disease: Signs and Symptoms of Untreated Lyme Disease. https://www.cdc.gov/lyme/signs_symptoms/index.html
- Centers for Disease Control and Prevention. (2021). "Diagnosis and Testing | Lyme Disease." Retrieved from https://www.cdc.gov/lyme/diagnosistesting/index.html.
- Centers for Disease Control and Prevention. (2022). "Lyme Disease." Retrieved from https://www.cdc.gov/lyme/index.html.
- Marques, A. R. (2010). Lyme Disease: A Review. Current Allergy and Asthma Reports, 10(1), 13-20.
- Steere, A. C., Malawista, S. E., Snydman, D. R., Shope, R. E., Andiman, W. A., Ross, M. R., ... & Steele, F. M. (1977). Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis & Rheumatism, 20(1), 7-17.
- Bani, S., Gautam, M., Sheikh, F. A., Khan, B., Satti, N. K., Suri, K. A., Qazi, G. N., & Patwardhan, B. (2006). Selective Th1 up-regulating activity of Withania somnifera aqueous extract in an experimental system using flow cytometry. Journal of Ethnopharmacology, 107(1), 107-115. doi: 10.1016/j.jep.2006.02.016.
- Frontiers. (2021). Withania somnifera (L.) Dunal (Ashwagandha) for the possible therapeutics and clinical management of SARS-CoV-2 infection: Plant-based drug discovery and targeted therapy. Retrieved from Frontiers website.
- Velickovic, M., Arsenijevic, A., Acovic, A., Arsenijevic, D., Milovanovic, J., Dimitrijevic, J., Todorovic, Z., Milovanovic, M., Kanjevac, T., & Arsenijevic, N. (2021). (2021). Galectin-3, Possible Role in Pathogenesis of Periodontal Diseases and Potential Therapeutic Target. Frontiers in Pharmacology, 12. https://doi.org/10.3389/fphar.2021.638258

Addendum

- Verhaegh, Dennis, et al. “The Role of Host Immune Cells and Borrelia Burgdorferi Antigens in the Etiology of Lyme Disease.” *European Cytokine Network*, vol. 28, no. 2, June 2017, pp. 70–84. *DOI.org (Crossref)*, https://doi.org/10.1684/ecn.2017.0396.
- O’Regan, Anthony, et al. *Interleukin-6 Use in COVID-19 Pneumonia Related Macrophage Activation Syndrome*. 2020. *DOI.org (Datacite)*, https://doi.org/10.13140/RG.2.2.36718.15681.
- Wolfert, Margreet A., and Geert-Jan Boons. “Adaptive Immune Activation: Glycosylation Does Matter.” *Nature Chemical Biology*, vol. 9, no. 12, Dec. 2013, pp. 776–84. *DOI.org (Crossref)*, https://doi.org/10.1038/nchembio.1403.
- Kinashi, Yusuke, and Koji Hase. “Partners in Leaky Gut Syndrome: Intestinal Dysbiosis and Autoimmunity.” *Frontiers in Immunology*, vol. 12, Apr. 2021, p. 673708. *DOI.org (Crossref)*, https://doi.org/10.3389/fimmu.2021.673708.
- Eliaz, Isaac, and Avraham Raz. “Pleiotropic Effects of Modified Citrus Pectin.” *Nutrients*, vol. 11, no. 11, Nov. 2019, p. 2619. *DOI.org (Crossref)*, https://doi.org/10.3390/nu11112619.

Thursday 2:45pm – 3:45pm

Naturopathic Treatment of Tick-Borne Disease: A Deep Dive into the Pathophysiology of Lyme Disease and Babesia and the MOAs of Herbal Intervention

Please scan this QR code on you mobile

or tablet device to access the session feedback survey

Naturopathic Treatment of Tick-borne Disease: a deep dive into the pathophysiology of Lyme disease and Babesia and the MOAs of Herbal Intervention