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Detox regulators and other aspects of detoxification

Nrf2= Nuclear erythroid 2-related factor 2 , the main detox regulator and its mates, MRPs, Keap1 and ARE, and its nemesis NF-kB

JANET KIM NOV 2022

Why do they get stuck?

Depends on how much and what's in the bucket?

Sometimes need a bit of imagination and creativity to see the map

It's often in the history

Hope and reassurance are important .Calm their limbic system down

What to consider in detoxification:

- Identify toxins if possible. Total toxin load. How much /what in the bucket?What needs to be detoxed first?
- Remove from toxins and don't add any more!!! At least have air filter/dehumidifier if mould is the toxin/reduce !
- Binders -which ones for what?
- Digesion/Well functioning GB/Drainage
- Toxic bile can interfere with drainage and damage SI,
- Bile and Gut microbiome helps with detox
- Robust phase 2 /3 important to remove the traffic jam
- Kidney function and its inhibitors esp Hg
- Slow down phase 1 required in some situations
- What could be getting in the way of the process?
- Limbic system support.What works for them?
- MCAS may need to treated first or at the same time
- Detox is something you do constantly not just once!
- Any amount of detox to reduce the burden in the bucket will help!!

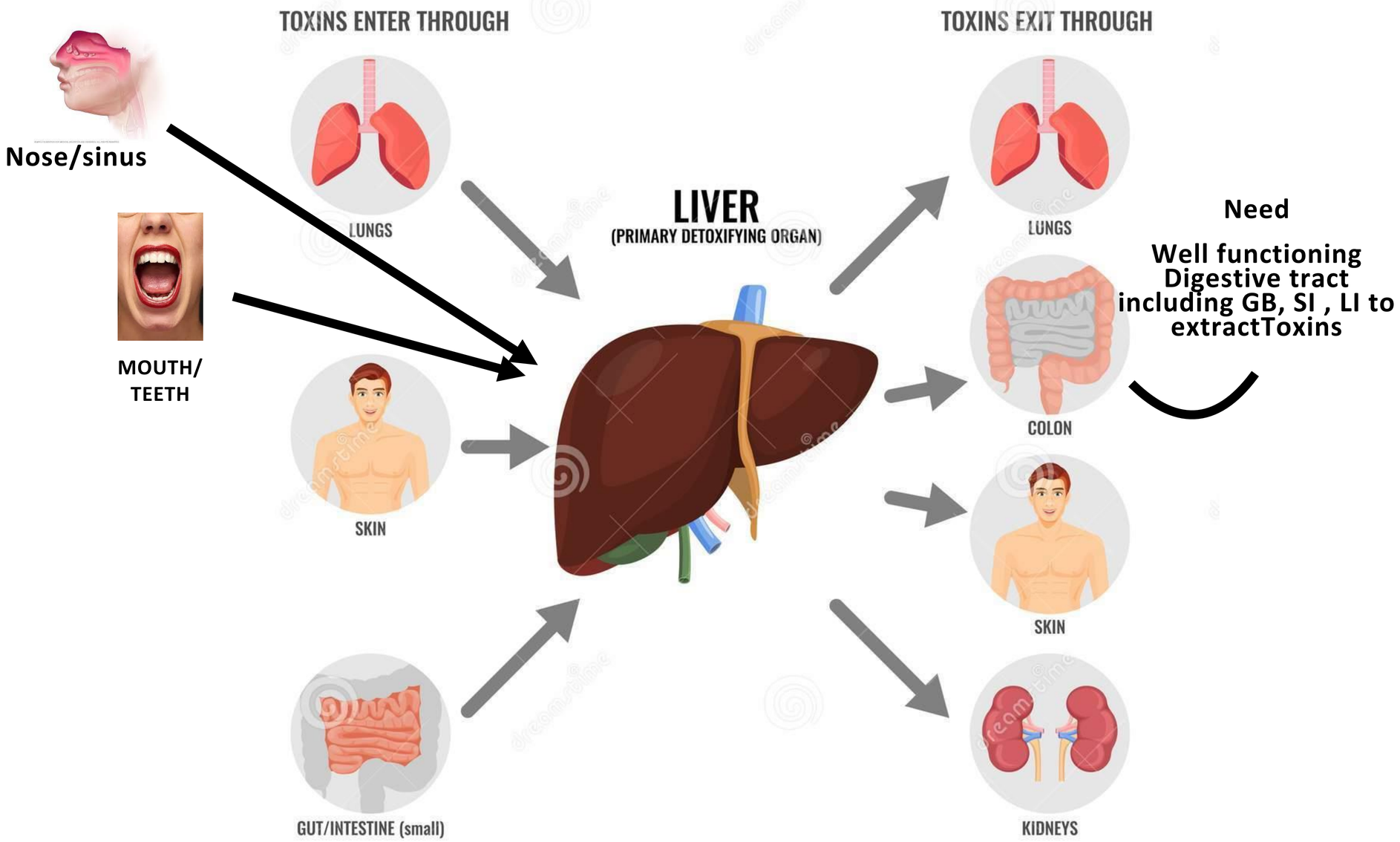
Inflammation /oxidative stress can be about how overburdened one is ..how full is their bucket?

Infections
Heavy metals
Trauma
Stress
Mould
Pesticides
Plastics
Other chemicals
Radiation
Other xenobiotics
Injuries
Pollution

Reducing
The burden bit by bit
can make a difference

AND How much antioxidant is left In their system??,

THE PROCESS OF DETOXIFICATION AND ELIMINATION



Need

Well functioning Digestive tract including GB, SI , LI to extractToxins

Toxins enter circulation from many organs then most eliminated via

liver(80%) ,

kidney,(18%)

skin(2%)

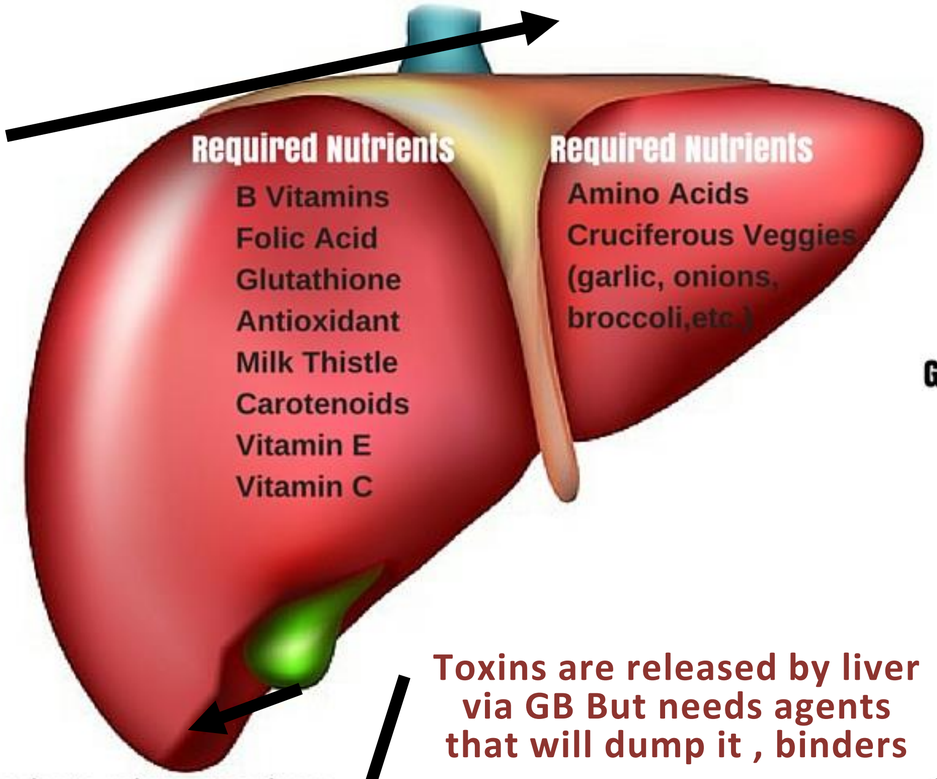
Liver

Coffee enema helps here

Detoxification Pathways

Toxins → Phase 1 → Phase 2 → Waste Products

Phase 3



Eliminated from the body via:

- Gallbladder → Bile → Bowels
- Kidneys → Urine

Mould blocks Nrf2 =detox pathway

Toxin List:

metabolic end products, micro-organisms, contaminants/pollutants, insecticides, pesticides, food additives, drugs, alcohol

Toxins are released by liver via GB But needs agents that will dump it , binders

Without binder toxins reabsorbed.

Toxic bile can cause SIBO

Contents today

- Inflammation/oxidative stress
- NF-kB/Nrf2/Keap1/ARE/MRPs(brief)
- Nrf2 stimulants/inhibitors(read in your own time)
- CIRS Dx/Rx template
- Perfect Storm scenario(read in your own time)
- SIBO/oxalates/glucuronidation/bilirubin
- Detoxification revisited
- CE/Sauna/castor oil pack/foot bath/Oil pulling/skin brushing etc

Abbreviations used :

- **Nrf2**:Nuclear factor erythroid 2-related factor 2, also known as nuclear factor erythroid-derived 2-like 2, is a transcription factor that in humans is encoded by the NFE2L2 gene
- **KEAP1**:Kelch-like ECH-associated protein 1
- **NQO1: NAD(P)H dehydrogenase (quinone 1):**NADH (Nicotinamide Adenine Dinucleotide plus Hydrogen) Quinone Oxidoreductase 1
- **HIF-1 :**Hypoxia inducible factor 1
- **NF-kB**: Nuclear factor kB
- **ARE**: The antioxidant response element (ARE) is a cis-acting enhancer sequence that mediates transcriptional activation of genes in cells exposed to oxidative stress
- **MRP**:Multidrug resistance Protein (1,2)
- **GSH**: glutathione
- **HO-1:**Heme oxygenase-1 (HO-1) is a Nrf2-regulated gene that **plays a critical role in the prevention of vascular inflammation**. It is the inducible isoform of HO, responsible for the oxidative cleavage of heme groups leading to the generation of biliverdin, carbon monoxide, and release of ferrous iron.
- **MMPs**: Matrix metalloproteinases (MMPs) are a group of enzymes that in concert are responsible for the degradation of most extracellular matrix proteins during organogenesis, growth and normal tissue turnover.
- **Hormetic**: A biphasic dose response to an environmental agent characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect. Eg. the reduction in energy as associated with 5:2 intermittent fasting or time-restricted eating is a hormetic stressor, meaning that it causes a very mild sort of damage to the body which elicits a much greater therapeutic effect in response.
- **eNOS** :endothelial nitric oxide synthase
- **NMDA**: N-Methyl-D-Aspartate

Inflammation/oxidative stress

To discuss this we need to start with inflammation and oxidative stress,the most common features of many chronic and acute diseases and complications and in part in carcinogenesis.

Most of our work involves mitigating inflammation and oxidative stress from toxicity and chronic infections.

Inflammation/oxidative stress

- Occurs when tissues are i**nfected or injured** by harmful stimuli such as **pathogens, damage, or irritants(toxicants), radiation , trauma . Oxidative stress involves the exposure of cells and/or tissues to reactive oxygen species (ROS)** generated by various intrinsic and extrinsic factors.
- Associated with a variety of disease states induced by **physical, chemical, biological, and psychological factors.**
- Two distinct forms of inflammation are distinguished: **acute and chronic**. Acute inflammation is self-limiting and beneficial to the host, but prolonged chronic inflammation is a common feature of many chronic diseases and complications.
- Exposure to **acute or chronic oxidative stress causes cellular damage and impairs** the normal physiological functions of various organs, causing a variety of diseases, such as acute organ failure, chronic degenerative diseases, and cancers.
- **Cytokines ,Immune cells, blood vessels, and molecular mediators ,gene actiavtion** are involved in this protective response.
- **Aim of inflammation is to limit and eliminate the causes** of cellular damage, clear and/or absorb necrotic cells and tissues, and initiate tissue repair and recovery. Ie healthiness

NF-kb

“This protein has a key function in regulating the human immune system, and its dysregulation has been linked to many chronic diseases including asthma, cancer, diabetes, rheumatoid arthritis, inflammation, and neurological disorders. Physiologically, many cytokines have been discovered that activate NF-κB”

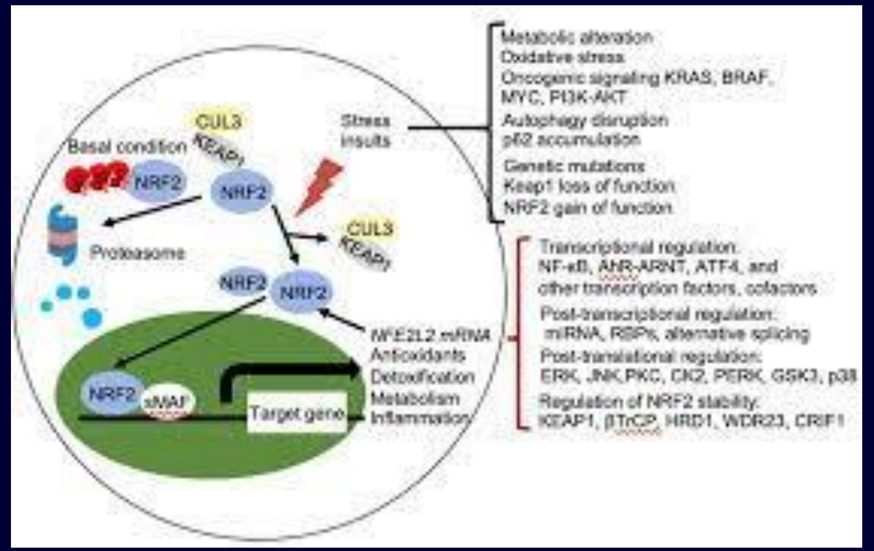
https://pubmed.ncbi.nlm.nih.gov/32421977/

“**Chronic stress** enhances the activation of NF-κB in response to inflammatory stimuli …“

https://pubmed.ncbi.nlm.nih.gov/25557189/

Nrf2

“Nrf2 is a key transcription factor controls many aspects of cell homoeostasis in response to oxidative and toxic insults. It mediates basal and induced transcription of phase II antioxidant proteins, which are responsible for the clearance of reactive oxygen species (ROS), providing protection against the accumulation of toxic metabolites. …This oxidative damage can be triggered by injury, toxicity ,infection, inflammation and involves the production of free radicals”.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC736990

Nrf2

Nrf2 is the main mitigator of oxidation/ inflammation /toxicity.

Nrf2 is a crucial Phase 2 liver detoxification regulator.

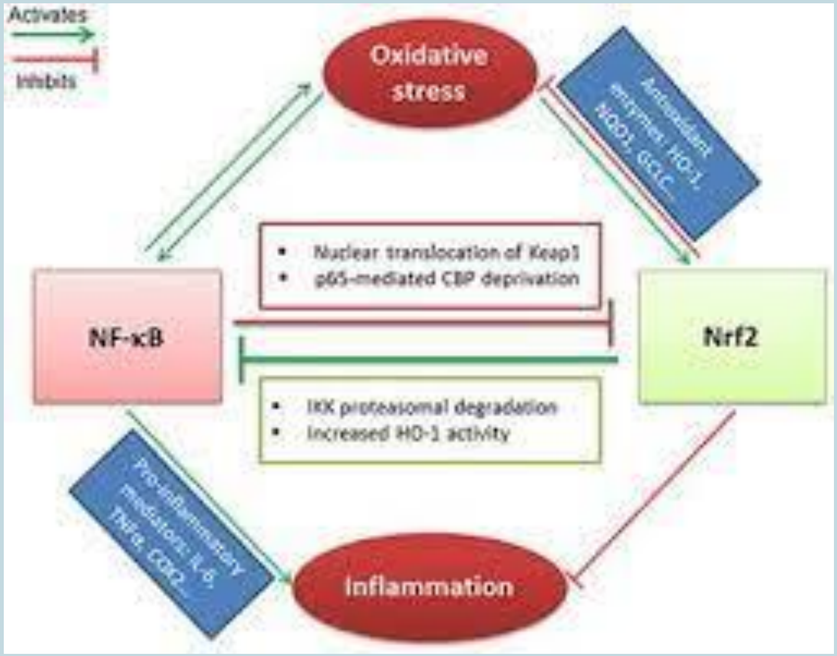
Toxins needs to be able to leave the body but mould blocks this by over stressing/stimulating Nrf2 pathway.

When Nrf2 is blocked or overstressed anti -oxidation becomes impossible

Reviving the detox pathway by metered Nrf2 stimulation can be a key to successful detoxification

Nrf2 and NF-kB are two key transcription factors that regulate cellular responses to oxidative stress and inflammation respectively.

- **Nrf2 and NF-κB** are key pathways regulating the fine balance of cellular redox status and responses to stress and inflammation.
- Imbalance between **Nrf2 and NF-κB** pathways is associated with a significant number of diseases ranging from neurodegeneration, autoimmune disorders and cancer.
- The interplay between these pathways occurs through a range of complex molecular interactions and can often depend on the cell type and tissue context. .



https://www.frontiersin.org/articles/10.3389/fimmu.2019.01004/full

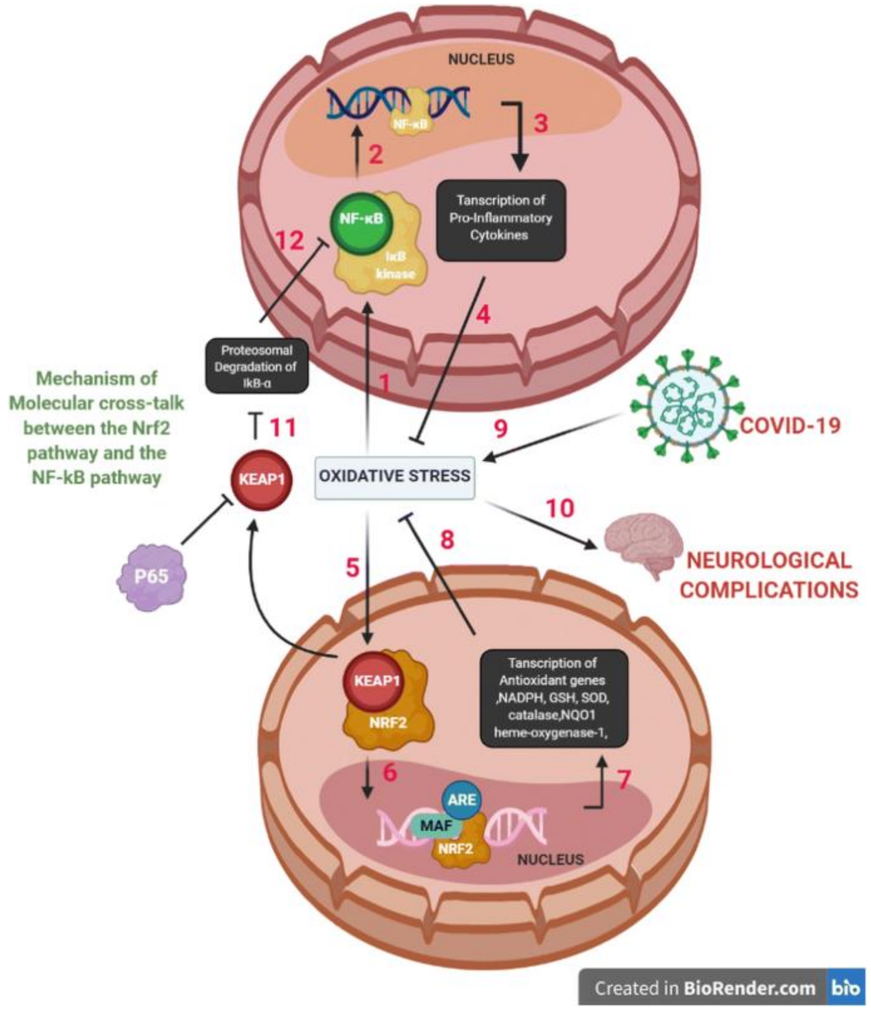
MOST INFLAMMATON/OXIDATIVE STRESS INVOLVES A DANCE BETWEEN NF-KB AND NRF2 .NF-KB INSTIGATES FIRE, NRF2 PUTS IT OUT.

- **NF-κB** complex is a key transcription factor that mediates immune responses to bacterial and viral infections, inflammation, toxicty, aspects of development, cell proliferation and protection against UV radiation, emotional stress .

- Pro-inflammatory cytokines such as tumour necrosis factor (TNF)α, interleukin (IL)-1β and bacterial lipopolysaccharide (LPS) are among the most potent **NF-κB** activators

- **NF-κB**, MAPK (mitogen-activated protein kinase), and JAK (janus kinase)-STAT (signal transducers and activators of transcription) signaling pathways are involved in the development of the classical pathway of such inflammation.

- The deficiency of **Nrf2** elevates the expression of **NF-κB**, leading to increased production of inflammatory factors," https://www.frontiersin.org/articles/10.3389/fcell.2021.809952/full



https://link.springer.com/article/10.1007/s12035-021-02344-7

2020;40(1):1-39. doi: 10.1615/CritRevImmunol.2020033210.

Inflammation, NF-κB, and Chronic Diseases: How are They Linked?

Ajaikumar B Kunnumakkara 1, Bano Shabnam 1, Sosmitha Girisa 1, Choudhary Harsha 2, Kishore Banik 1, Th Babita Devi 2, Ruplekha Choudhury 2, Henamayee Sahu 2, Dey Parama 2, Bethsebie L Sailo 1, Krishan Kumar Thakur 1, Subhash C Gupta 3, Bharat B Aggarwal 4
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PMID: 32421977 DOI: 10.1615/CritRevImmunol.2020033210

Abstract

Most chronic diseases, caused by lifestyle factors, appear to be linked to inflammation. **Inflammation is activated mechanistically, and nuclear factor-κB (NF-κB) is a significant mediator**. NF-κB, one of the most studied transcription factors, was first identified in the nucleus of B lymphocytes almost three decades ago. This protein has a **key function in regulating the human immune system, and its dysregulation has been linked to many chronic diseases including asthma, cancer, diabetes, rheumatoid arthritis, inflammation, and neurological disorders.** Physiologically, many cytokines have been discovered that activate NF-κB. Pathologically, environmental carcinogens such as cigarette smoke, radiation, bacteria, and viruses can also activate this transcription factor. NF-κB activation controls expression of more than 500 genes, and most are deleterious to the human body when dysregulated. More than 70,000 articles have been published regarding NF-κB. This review emphasizes the upside and downside of NF-κB in normal and disease conditions and the ways in which we can control this critical transcription factor in patients.

Int J Mol Sci. 2017 Dec; 18(12): 2772.
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PMCID: PMC5751370
PMID: 29261130

Nrf2, the Master Regulator of Anti-Oxidative Responses

Sandra Vomund,1,† Anne Schäfer,2,† Michael J. Parnham,1 Bernhard Brüne,1,2 and Andreas von Knethen1,2,*

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Abstract

Tight regulation of inflammation is very important to guarantee a balanced immune response without developing chronic inflammation. One of the major mediators of the resolution of inflammation is the transcription factor: the nuclear factor erythroid 2-like 2 (Nrf2). Stabilized following oxidative stress, Nrf2 induces the expression of antioxidants as well as cytoprotective genes, which provoke an anti-inflammatory expression profile, and is crucial for the initiation of healing. In view of this fundamental modulatory role, it is clear that **both hyper- or hypoactivation of Nrf2 contribute to the onset of chronic diseases.** Understanding the tight regulation of Nrf2 expression/activation and its interaction with signaling pathways, known to affect inflammatory processes, will facilitate development of therapeutic approaches to prevent Nrf2 dysregulation and ameliorate chronic inflammatory diseases. We discuss in this review the principle mechanisms of Nrf2 regulation with a focus on inflammation and autophagy, extending the role of dysregulated Nrf2 to chronic diseases and tumor development.

2015 Feb 25;67(1):1-18.

Nrf2, a master regulator of detoxification and also antioxidant, anti-inflammatory and other cytoprotective mechanisms, is raised by health promoting factors

Martin L Pall 1, Stephen Levine 2
Affiliations expand
PMID: 25672622

Abstract

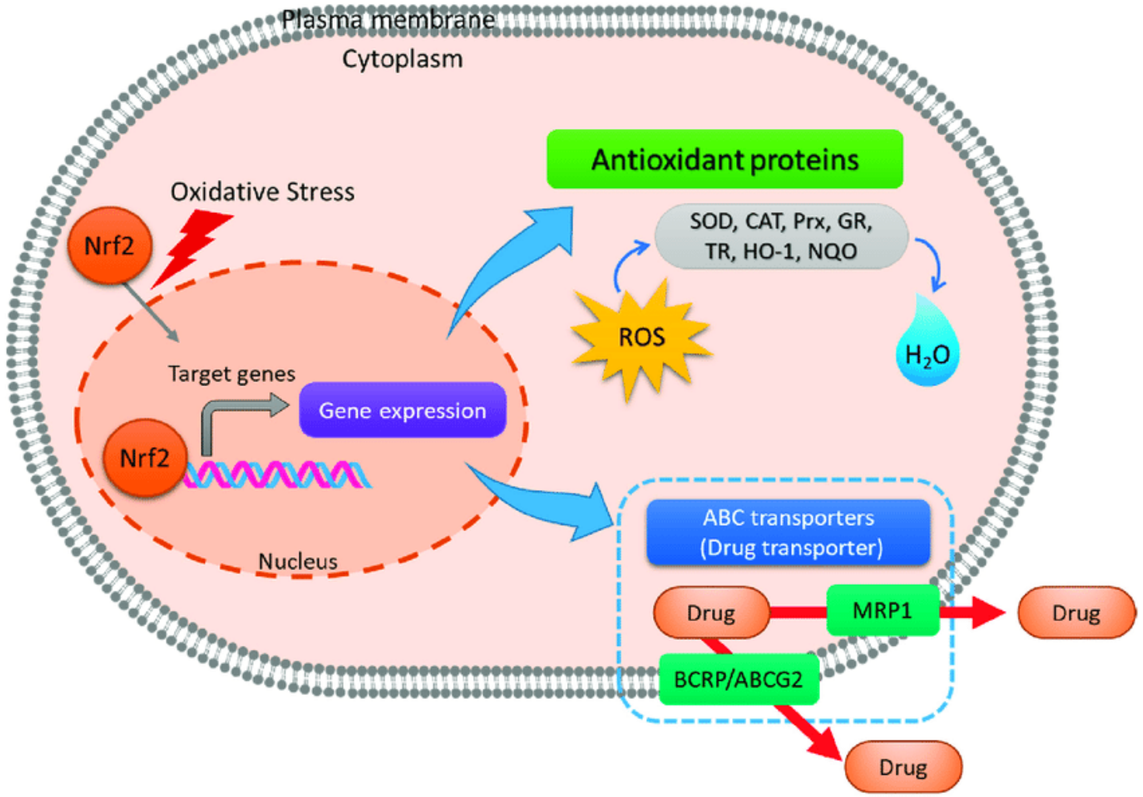
The transcription factor Nrf2, nuclear factor erythroid-2-related factor 2, activates the transcription of over 500 genes in the human genome, most of which have cytoprotective functions. **Nrf2 produces cytoprotection by detoxification mechanisms leading to increased detoxification and excretion of both organic xenobiotics and toxic metals; its action via over two dozen genes increases highly coordinated antioxidant activities; it produces major anti-inflammatory changes; it stimulates mitochondrial biogenesis and otherwise improves mitochondrial function;** and it stimulates autophagy, removing toxic protein aggregates and dysfunctional organelles. Health-promoting nutrients and other factors act, at least in part by raising Nrf2 including: many phenolic antioxidants; gamma- and delta-tocopherols and tocotrienols; long chain omega-3 fatty acids DHA and EPA; many carotenoids of which lycopene may be the most active; isothiocyanates from cruciferous vegetables; sulfur compounds from allium vegetables; terpenoids. Other health promoting, Nrf2 raising factors include low level oxidative stress (hormesis), exercise and caloric restriction. Raising Nrf2 has been found to prevent and/or treat a large number of chronic inflammatory diseases in animal models and/or humans including various cardiovascular diseases, kidney diseases, lung diseases, diseases of toxic liver damage, cancer (prevention), diabetes/metabolic syndrome/obesity, sepsis, autoimmune diseases, inflammatory bowel disease, HIV/AIDS and epilepsy. Lesser evidence suggests that raising Nrf2 may lower 16 other diseases. Many of these diseases are probable NO/ONOO(-) cycle diseases and Nrf2 lowers effects of NO/ONOO(-) cycle elements. The most healthful diets known, traditional Mediterranean and Okinawan, are rich in Nrf2 raising nutrients as apparently was the Paleolithic diet that our ancestors ate. Modern diets are deficient in such nutrients. Nrf2 is argued to be both lifespan and healthspan extending. Possible downsides to too much Nrf2 are also discussed. Nrf2 is not a magic bullet but is likely to be of great importance in health promotion, particularly in those regularly exposed to toxic chemicals.

NRF2 REGULATES OXIDATIVE/XENOBIOTIC STRESS , REPRESSES INFLAMMATION IN A HORMETIC MANNER

- Nrf2 regulates the expression of **phase II detoxifying enzymes including, NAD(P)H quinone oxidoreductase 1(NOQ1), glutathione peroxidase, ferritin, heme oxygenase-1 (HO-1),** and other **antioxidant genes** that protect cells from various injuries via their anti-inflammatory effects,
- Nrf2 increases the **supply of cysteine** by directly activating *Slc7a11*, the gene encoding the xCT subunit of system xl**>>GSH synthesis**
- In addition to **GSH synthesis,** Nrf2 plays a role in **GSH maintenance.**
- Nrf2 carries out its action through **attaching itself to ARE** in nucleus of cytosol
- **Keap1** acts as a sensor of chemical and oxidative stresses as well as a negative regulator of Nrf2
- Under non stressed conditions, **Keap1** facilitates the **ubiquitination (UB) and proteasomal breakdown** of Nrf2. In **acute stress Keap 1 activates Nrf2.**
- **Chronic stressed conditions**, and **Keap 1 genetic mutation** are responsible for Nrf2 activation **not** being turned off **causing more damage.**
- ~~Aim to protect cells from various injuries via their anti-inflammatory effects, thus influencing~~ the course of disease.
- Nrf2 has a half-life of approximately 20 min.

NRF2 ALSO NEEDS HELP BY MRPS(X9)

- Nrf2 stimulate **production** of **GSH** and **multidrug resistance protein 1 (Mrp1**)enables **utilisation and recycles it.**
- **Glutathione conjugated xenobiotics ,metabolites, drugs are exported from the target tissues by Mrp transporter.**
- **Mrp1** responds to oxidative stress and recycling exported **GSH via GSH reductase**
- Cancer cells that showed lowered Mrp1 also demonstrated lowerNrf2



https://www.researchgate.net/figure/Effect-of-Nrf2-gene-knockout-on-MRP1-expression-A-Immunohistochemistry-results-of_fig2_346368515

ALTOGETHER HELPS INFLAMMATORY RESPONSE

NK-fB

Nrf2

ARE

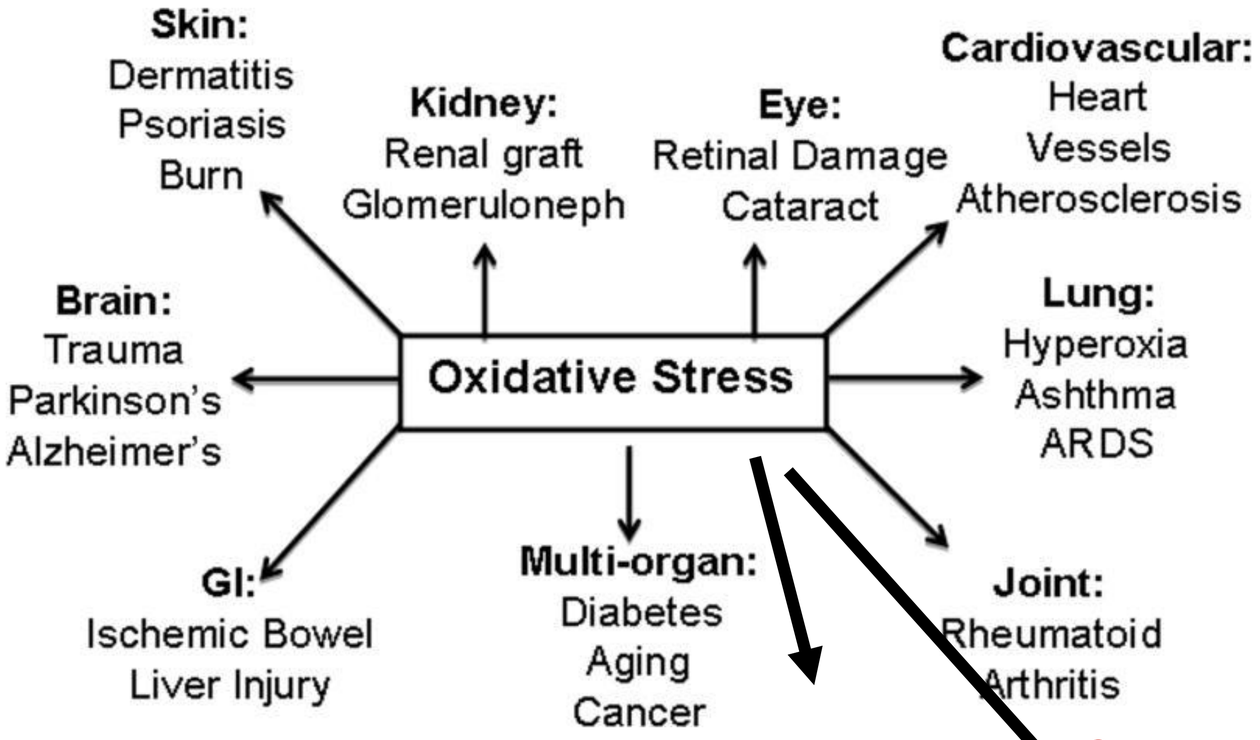
Mrps

GSH,
Antioxidant
enzymes,genes

Inflammation
Oxidative stress
Toxicity

Keap1

NRF2 RELATED CONDITIONS



Multiorgan inflammation : CIRS , TBD

Cancer

in these conditions Nrf2 May not work

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3773280/ (Modified)

molecules MDPI

Molecules. 2020 Nov; 25(22): 5474.
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PMCID: PMC7700122
PMID: 33238435

An Overview of Nrf2 Signaling Pathway and Its Role in Inflammation

Sarmistha Saha,1,* Brigitta Buttari,1 Emiliano Panieri,2 Elisabetta Profumo,1 and Luciano Saso2
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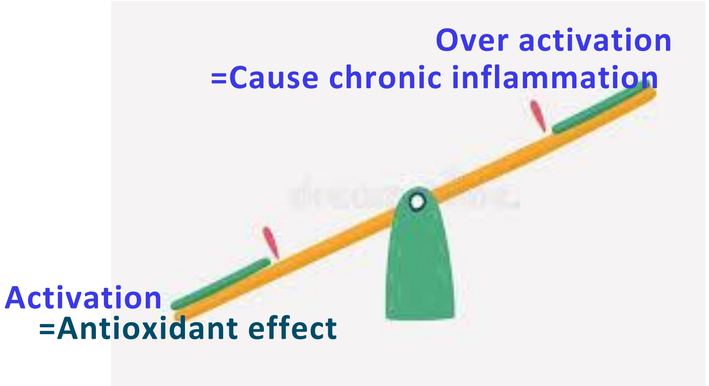
Abstract

Inflammation is a key driver in many pathological conditions such as allergy, cancer, Alzheimer's disease, and many others, and the current state of available drugs prompted researchers to explore new therapeutic targets. In this context, accumulating evidence indicates that the transcription factor Nrf2 plays a pivotal role controlling the expression of antioxidant genes that ultimately exert anti-inflammatory functions. Nrf2 and its principal negative regulator, the E3 ligase adaptor Kelch-like ECH- associated protein 1 (Keap1), play a central role in the maintenance of intracellular redox homeostasis and regulation of inflammation. Interestingly, Nrf2 is proved to contribute to the regulation of the heme oxygenase-1 (HO-1) axis, which is a potent anti-inflammatory target. Recent studies showed a connection between the Nrf2/antioxidant response element (ARE) system and the expression of inflammatory mediators, NF-κB pathway and macrophage metabolism. This suggests a new strategy for designing chemical agents as modulators of Nrf2 dependent pathways to target the immune response. Therefore, the present review will examine the relationship between Nrf2 signaling and the inflammation as well as possible approaches for the therapeutic modulation of this pathway.

SO EXCESS NRF2 ACTIVATION IS NOT ALWAYS A GOOD THING?

- Activation of Nrf2, requires **a threshold** of an oxidative response/ inflammation so the body can create an **adaptive response**, and to create antioxidants including GSH.
- Eg acute exercise - exercised muscles can adapt and better prepare for another/harder workout session .
- But marathon runners can have lower bone density and attributed to inflammation.
- If Nrf2 becomes over /chronically activated from chronic infections/toxins (eg. mould, lyme, EBV, metals other toxins) i**t can perpetuate inflammation instead as it fails to 'turn off '**
- Chronic Inflammatory Response Syndrome (**CIRS**), is a perfect example of Nrf2 being **over activated and patients getting worse after Nrf2 activation.** Nrf2 plays a key role in perpetuating the chronic inflammatory process by continued infiltration of inflammatory cells to inflamed tissue. **Careful balancing work** in CIRS is the key.

ÒME CHRONIC PATIENTS GET SICKER DURINC TREATMENT/DETOX!!??



NRF2 BENEFITS CELLULAR OXYGENATION AGAINST

- Nrf2 can protect the body against **hypoxia.**
- Those with **CIRS** have low levels of oxygen because **Nrf2 effect is blocked** by chronic stimulation leading to **low levels of VEGF, HIF1, and HO-1. May be one of the courses of Aerobic exercise intolerance/ post exertional fatigue(besides rise in C4a,decrease in MSH > >capillary hypo perfusion in CIRS)**
- Normally in healthy people with hypoxia, improve levels of Nrf2/HO-1 and VEGF/eNOS, thus preventing brain damage, but this doesn't seem to happen in CIRS.
- **Hypoxia (low HIF1) in CIRS** may also lead to a **leaky blood brain barrier** because of Nrf2 dysregulation.
- Salidroside (found in Rhodiola) acts on Nrf2 and helps with hypoxia by increasing VEGF and HIF1.(Nrf2 protects against lactate buildup in the heart.
- Nrf2 can also prevent hypoxia-induced Altitude Motion Sickness (AMS).

Just a bit more on Nrf2..

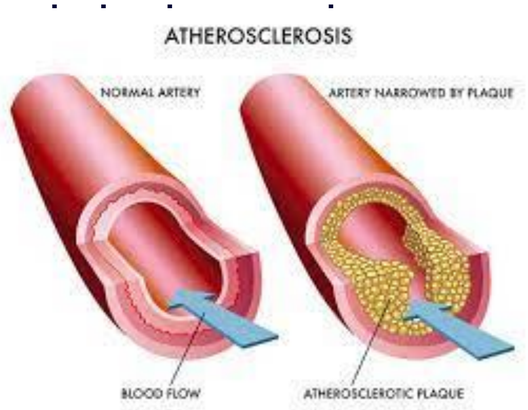
Examples benefitted by Nrf2 Activation

- Aging
- Autoimmunity and Overall Inflammation
- Autism
- Cancer and Chemoprotection (including EMF Exposure)
- Depression and Anxiety /PTSD
- Drug Exposure (Alcohol, NSAIDs)
- Exercise and Endurance Performance
- Gut Disease (ie SIBO, Dysbiosis, Ulcerative Colitis)
- Kidney Disease (ie Acute Kidney Injury, Chronic Kidney Disease, Lupus Nephritis)
- Liver Disease (ie Alcoholic Liver Disease, Acute Hepatitis, Nonalcoholic Fatty Liver Disease, , Cirrhosis)
- Lung Disease (ie Asthma, Fibrosis)
- Metabolic And Vascular Disease (ie Atherosclerosis, Hypertension, Stroke, Diabetes)
- MCAS (esp Resveratrol)
- Neurodegeneration (ie Alzheimer's, Parkinson's, Huntington's and ALS)
- Pain (ie Neuropathy)
- Skin Disorders (ie Psoriasis, UVB/Sun Protection)
- Toxin Exposure (Arsenic, Asbestos, Cadmium, Fluoride, Glyphosate, Mercury, Sepsis, Smoke)
- Vision (ie Bright Light, Sensitivity, Cataracts, Corneal Dystrophy)


Detailed examples of Nrf 2 will be skipped -we can look at later

Nrf2 improves vascular system

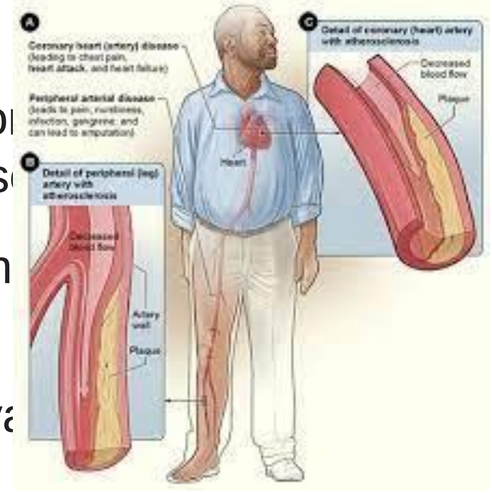
- Nrf2 activation can protect against heart disease such as hypertension and atherosclel acetylcholine relaxing vascular system while lowering cholesterol-induced stress.
- Acute activation of Nrf2 (such as exercise), can strengthen the heart, although over-act the chance of heart disease by damaging myocardium.
- Nrf2 plays a big role in balancing iron and can protect from high levels of iron by acting which is associated iron homeostasis Nrf2 may also help with Sickle Cell Disease .



- Nrf2 dysfunction may be a reason for endotoxemia (such as having dysbiosis or lectins) induced hypertension.
- It can protect against amphetamine induced damage to the vascular system.

Nrf2 and atherosclerosis

- Oxidative stress represents a key player in the pathophysiology of atherosclerosis when ongoing switched off . Hence artheroscolerosis is now partly though of inflammatory cause (monoclonal ab, Metformin under clinical trial for this reason)
- Imbalance between pro- and antioxidant agents drives to an overproduction of ROS, which pro peroxidation, cell death, and endothelial dysfunction, initial steps in the development of atheros
- Overall, both, Nrf2 and HO-1 have shown to protect against initial atherosclerotic injury through anti-inflammatory, or even immunomodulatory properties.
- Compounds like resveratrol or sulforaphane are also being tested due to their potential to activa pathway. Some of these molecules have shown promising results at the preclinical side.



- On the other hand, Nrf2 may also enhance atherosclerosis through additional mechanisms that need to be further characterized but likely to be due to over/chronic stimulation of Nrf2.

Nrf2 and ageing

- Nrf2 decreases with aging
- A tiny amount of stress /toxin can increases the cell to stimulate Nrf2 and could be beneficial :)eg Intermittent fasting, exercise , cold exposure.
- Nrf2 is able to increase the lifespan of cells by increasing their levels of mitochonrdia, antioxidants and reduce the cells' ability to die.
- Nrf2 stops stem cells from dying and helps them regenerate.
- Nrf2 improves wound healing.

Nrf2 and brain inflammation

Nrf2 can protect against and help neuroinflammation.

Nrf2 can help with a variety of Central Nervous System (CNS) disorders:

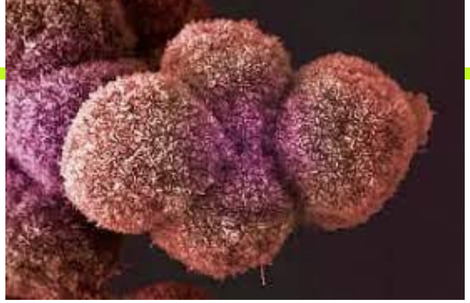
- Alzheimer’s Disease (AD) - reduces amyloid beta stress on mitochondria
- Amyotrophic Lateral Sclerosis (ALS)
- Huntington's Disease (HD)
- Multiple Sclerosis (MS)
- Nerve Regeneration
- Parkinson’s disease (PD) - protects dopamine
- Spinal Cord Injury (SCI)
- Stroke (ischemic and hemorrhagic) - help hypoxia
- Traumatic Brain Injury

Nrf2 has shown reduce neuroinflammation in teenagers with Autism Spectrum Disorders (ASD).

Nrf2 and Depression

- In depression, it is common to see inflammation in the brain (esp in the prefrontal cortex and hippocampus) as well as decreased Brain Derived Neurotropic Factor(BDNF.)
- Nrf2 may improve depressive symptoms by reducing neuroinflammation and increasing BDNF levels.
- Eg , PTSD can be helped by activation of Nrf2 , Arginine based chemical Agmatine can reduce depression by increasing neurotransmitters and BNDF in hippocampus which is another Nrf2 activation mode.

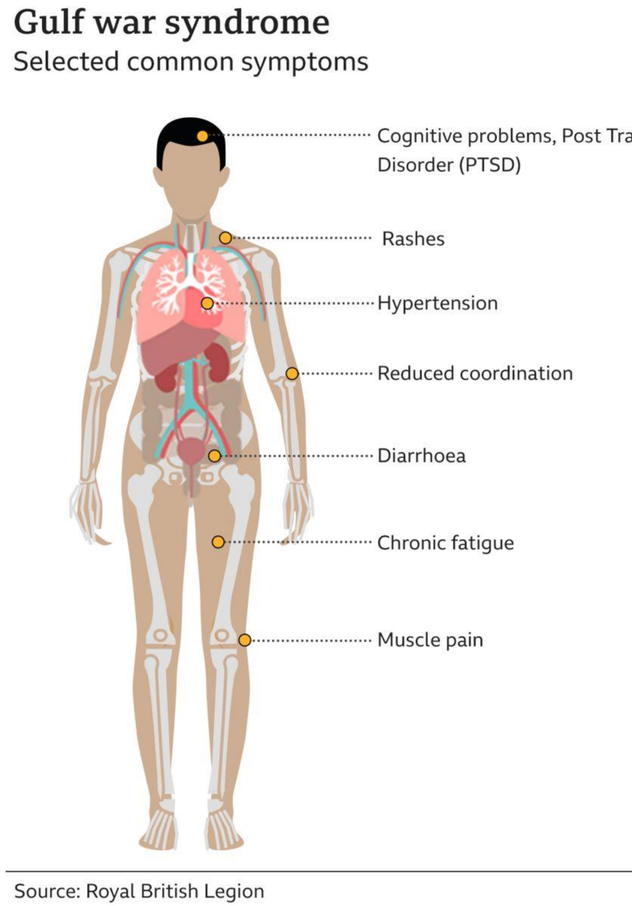
Nrf2 and cancer



- Nrf2 2 is both a tumour suppressor, as well as tumour promoter. Eg Nrf2 can protect against cancer induced by toxins, but Nrf2 overexpression is found in cancer cells
- Transient Nrf2 activation, by its specific activators, has protective roles against carcinogenesis and cancer development.
- Chronic Nrf2 activation can be detrimental to cancers.
- Nrf2 promotes cancer cell growth and proliferation. Cancer cells differ from normal cells by its enormous growth and proliferative capacity, which is often observed with Nrf2 overactivation. The reduced state of GSH is indispensable for cell proliferation due to its detoxification, antioxidant defense function, etc.
- Permanent activation of Nrf2 promotes various cancer properties, comprising malignant progression, chemo/radio resistance, and poor patient prognosis. Epigenetic alterations in the Keap1 gene donate a growth advantage to cancer cells and are correlated with poor clinical prognosis in cancer patients . The promoter hypermethylation of Keap1 that can lead to reduction of Keap1 expression and Nrf2 accumulation in the nucleus has been identified in malignant glioma , lung , prostate, colorectal, gastric ,and breast cancers

Nrf2 and pain

- Gulf War Illness (GWI) is a prominent condition affecting Gulf War Veterans is a cluster of multi system illness symptoms that include fatigue, headaches, joint pain, indigestion, insomnia, dizziness, respiratory disorders, and memory problems.
- Nrf2 may improve symptoms of GWI by decreasing hippocampal and overall inflammation, as well as pain. Eg Medical Cannabis
- Nrf2 can help with pain from physical nerve injury and improve nerve injury from diabetic neuropathy.
- Medical Cannabis can reduce pain via Nrf2 pathway



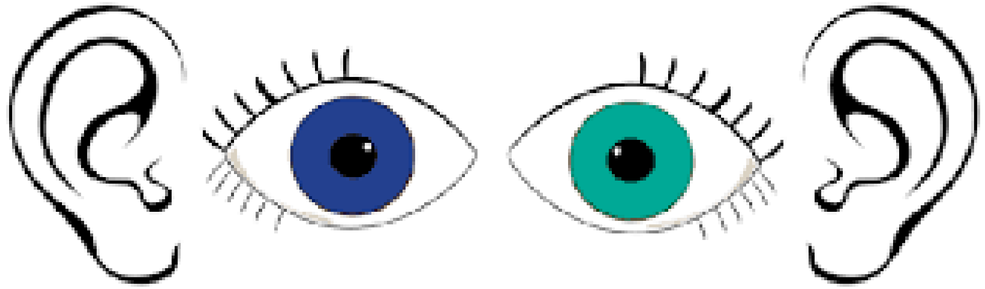
Nrf2 and diabetes

- Hyperglycemia causes oxidative damage the the cells by disruption of mitochondrial function.
- Nrf2 activation can protect against hyperglycemia's damage to the cell, thus preventing cell death.
- Nrf2 activation may also protect, restore, and regenerate pancreatic beta-cell function, while decreasing insulin resistance.
- Berberine activates Nrf2 nuclear translocation and is identified as a potential anti-diabetic herbal medicine due to its beneficial effects on insulin sensitivity, glucose metabolism and glycolysis.

Nrf2 and vision , hearing

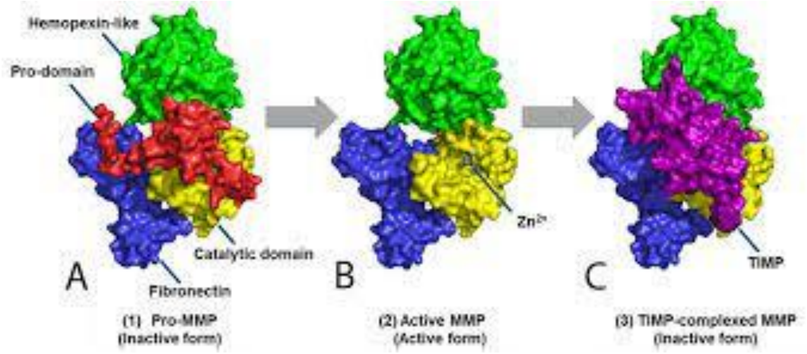
- Nrf2 may protect against damage to the eye from diabetic retinopathy.
- It may also prevent the formation of cataracts.
- It can protect photoreceptors against light-induced death.
- Nrf2 also protects the cochlea from hearing loss. Oxidative stress and the imbalance of redox homeostasis caused by ROS are important factors for cochlear injury.While oxidative stress is closely related to hair cell apoptosis through mitochondrial pathway in NIHL.Nrf2 deficiency or decreased expression is involved in the occurrence and development of ARHL.

NIHL: noise induced hearing loss
ARHL age-related hearing loss



Nrf2 and gut via inhibiting MMPs

- MMPs are the main group of enzymes responsible for the collagen and other protein degradation in extracellular matrix (ECM).
- MMPs are widely present in the extracellular matrix . -involved in physiological and pathological processes such as cell proliferation, migration, differentiation, wound healing, angiogenesis, apoptosis, and metastasis.
- Nrf2/HO-1 axis inhibits MMP-9 in macrophages and MMP-7 in human intestinal epithelial cells, and this is beneficial in the treatment of inflammatory bowel disease such as Ulcerative Colitis .
- Nrf2 can help protect the gut microbiome homeostasis.
- For example, lactobacillus probiotics will activate Nrf2 to protect the gut against oxidative stress.
- In inflammation the regulation of MMPs is affected directly by the Nrf2 pathway or indirectly through the Nrf2-influenced NF-κB pathway.



Nrf2 and sex organs

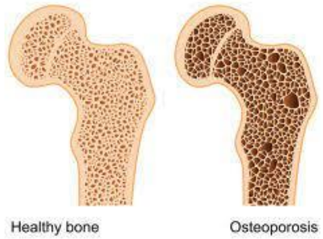
- Nrf2 may protect the testicles and maintain sperm count from damage in those with diabetes.
- Men with Nrf2 polymorphism sustain sperm damage from smoking(Turkish study)
- Nrf2 may help with Erectile Dysfunction (ED).
- Mucuna, Tribulus, and Ashwaganda may improves sexual function through Nrf2 activation.

Nrf2 and viral infections

- Nrf2 reduces symptoms with Dengue fever
- Nrf2 may also help those with HIV.
- Nrf2 may protect against the oxidative stress from Adeno-Associated Virus (AAV) and *H. Pylori*.
- Lindera Root can suppresses Hepatitis C virus by Nrf2 activation.
- Nrf2 has been found to be reduce inflammatory damage in Covid Sars2(Sulforaphane)

Nrf2 and bones, muscles

- Oxidative stress can lead to bone mass and strength loss, which is common in osteoporosis.
- Nrf2 activation may be able to enhance antioxidants in bones and prevent bone aging.
- Nrf2 may also prevent muscle loss and improve Duchenne Muscular Dystrophy (DMD).
- Nrf2 deficiency tended to increase osteoblastic markers and significantly enhanced osteoclastic markers in sham-operated animals indicating an increased bone turnover with a main effect on bone resorption.
- Poor Bone density in athletes who do prolonged exercises has been discussed

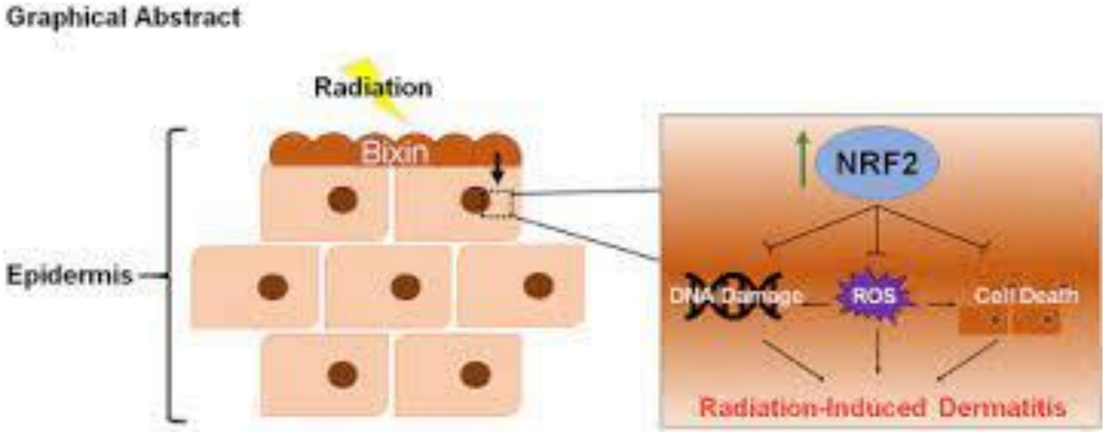


Nrf2 protection against toxins-

- Nrf2 is an innate trigger to protect the cells against foreign substances and enhance detox capacity to toxins by increasing multidrug resistance-associated proteins (MRPs, proteins which help push chemicals out of the cell),
- eg Nrf2 is activated upon cigarette smoke inhalation, as a way for the lungs to detox.(but ongoing smoking causes Nrf2 overstimulated resulting in cancer in some). Chronic taxing of this system (via something like chronic smoking) and depletes the lungs of glutathione.
- If Nrf2 isn't over taxed, its activation of it is a potent way to protect the liver from toxicity, eg Nrf2 can protect the liver against Arsenic hepatotoxicity.
- Nrf2 protects the brain and liver against alcohol consumption, eg protects against acetaminophen toxicity.

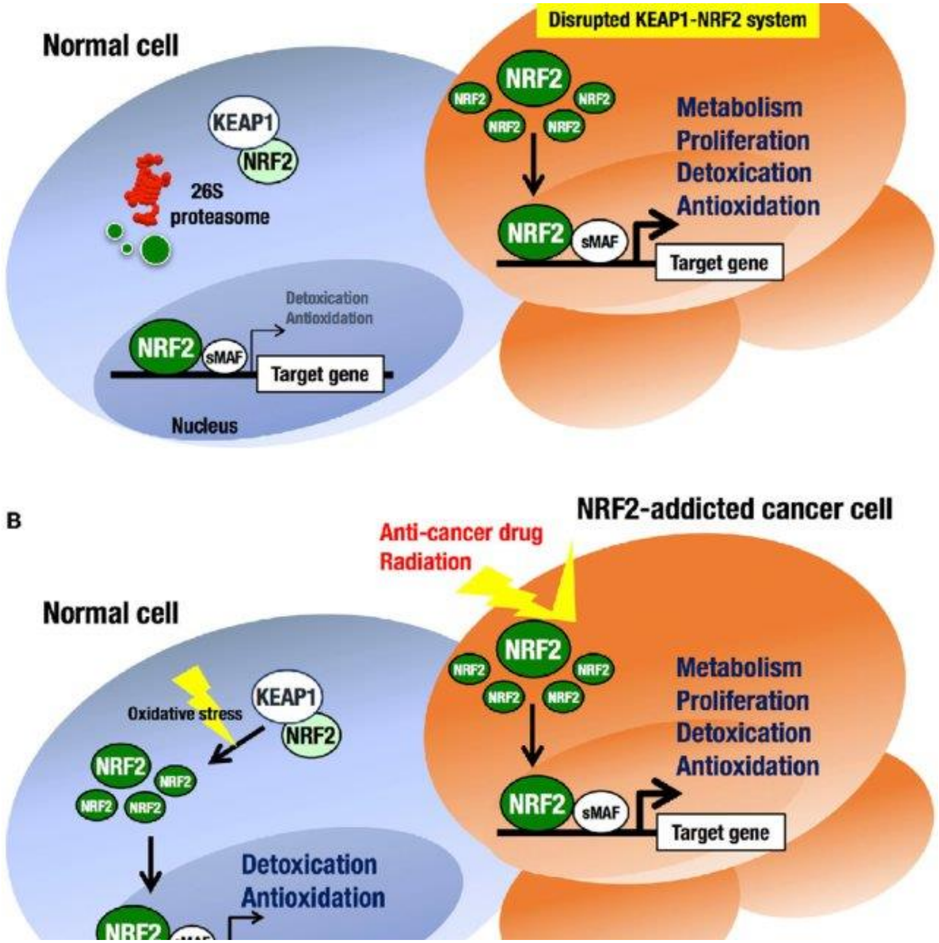
Nrf2 and radiation

- **UV irradiation-induced skin damage is more severe in Nrf2-knockout than in WT mice and the MMP-9 level is significantly higher, indicating that Nrf2 reduces MMP-9 expression.**
  - **Therefore Nrf2 protects against cellular damage of blue light and of UVA/B from the sun.eg tired Nrf2 makes it easier for you to get sunburnt. (why we have so much skin cancer in Australia? Just the ozone issue)**
  - **Nrf2 protects collagen in reaction to UV radiation.**



https://www.sciencedirect.com/science/article/pii/S2213231720309198

Nrf2 Overstimulation: too much of a good thing can be BAD

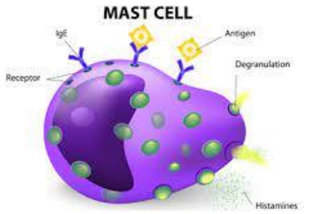


https://www.researchgate.net/figure/Difference-in-NRF2-activation-between-normal-cells-and-NRF2-addicted-cancer-cells-A_fig1_316703001

Nrf2 and allergies, MCAS

- Vit E prevents Nrf2-suppression by allergen in asthmatic alveolar macrophages *in vivo.*
- Nrf2 Suppresses Allergic Lung Inflammation by Attenuating the Type 2 Innate Lymphoid Cell Response

However it does have parodic reaction to allergies Nrf2 can also mitigate with allergies, by silencing Th1/Th17 cytokines and increasing TH2 cytokines-exacerbating allergies



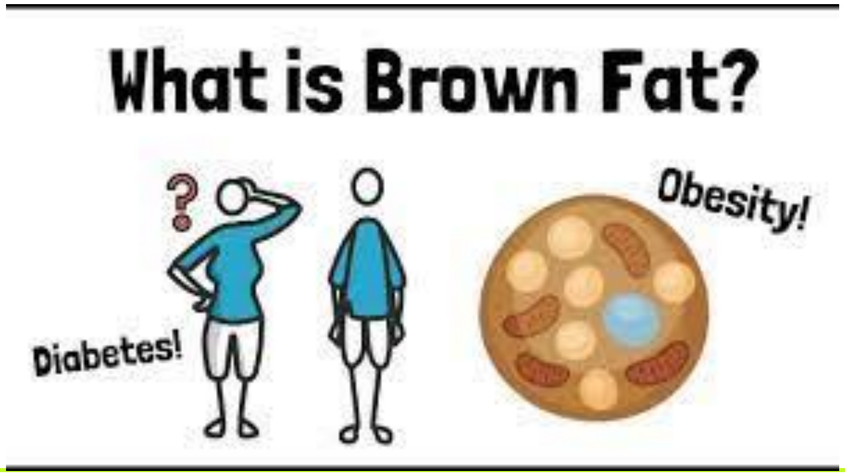
- Nrf2 activation modulate transcription in human MCs in response to pro-inflammatory stressors.
- Resveratrol was found to inhibit mast cell via Nrf2 pathway.
- Nrf2 inhibits MC degranulation and MC-mediated inflammation by promoting SIRT4, and SIRT4 over-expression and inhibits the mitochondrial metabolism of MCs. In this study they used anti-inflammatory agent 4-Octyl Itaconate .(4-Octyl Itaconate is a cell-permeable Itaconate derivative. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of Keap1.)

Others: Nrf2 protection against Other oxidative stress/inflammation

- Nrf2 activation by astragalus can decrease inflammatory cytokines (such as IL-8) in psoriasis.
- Nrf2 can also reduce inflammation in arthritis.
- It can reduce inflammation and fibrosis (via TGFb1) of the liver, kidney, and lungs- beneficial in CIRS!!.
- Nrf2 is able to reduce the oxidative stress of Advanced Glycation End products(AGEs) on the body.
- Nrf2 can also protect the body against high amounts of heat-based stress (40ºC or higher) -but sauna stimulates it ??
- Nrf2 is activated upon initial cigarette smoke inhalation, but ongoing smoking causes Nrf2 overstimulated resulting in cancer in some. Chronic taxing of this system via something like chronic smoking and depletes the lungs of glutathione can be detrimental.
- Nrf2 can protect the liver against Arsenic hepatotoxicity unless overtaxed.
- Nrf2 protects the brain and liver against alcohol consumption

Nrf2 and Obesity

- Nrf2 may possibly help with obesity by its ability to regulate factors that work on fat accumulation in the body.
- Nrf2 activation (with sulforaphane) can increase inhibit of Fatty Acid Synthesis (FAS) and Uncoupling Proteins (UCP), leading to better less fat accumulation and more brown fat (fat that has more mitochondria).



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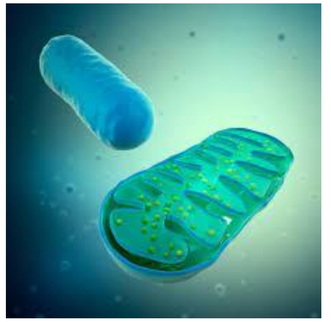
Nrf2 Enhances Mitochondria And Exercise Performance



- Nrf2 activates ATP as well as enhanced utilization of fat and oxygen .
- Nrf2 is necessary for biogenesis of mitochondria
- Nrf2, enables mitochondria to run on glucose, instead of fat. Aerobic exercise tolerance cases!)
- Nrf2 activation is crucial for benefitting from exercise and improve exercise tolerance
- Nrf2's enable moderate /HIIT HIST exercise types to increase mitochondrial function (amplified with CoQ10, Cordyceps, and Caloric Restriction). See my Nrf2 post exercise recipe later!
- Very intensive / prolonged exercise may turn Nrf2 off by increasing synthesis of super-oxide dismutase (SOD) and heme-oxygenase-1 (HO-1). Ie, perpetuating oxidation instead of turning it off.
- Nrf2 deletion makes exercise unhealthy for the body(Nrf2 KO mice)

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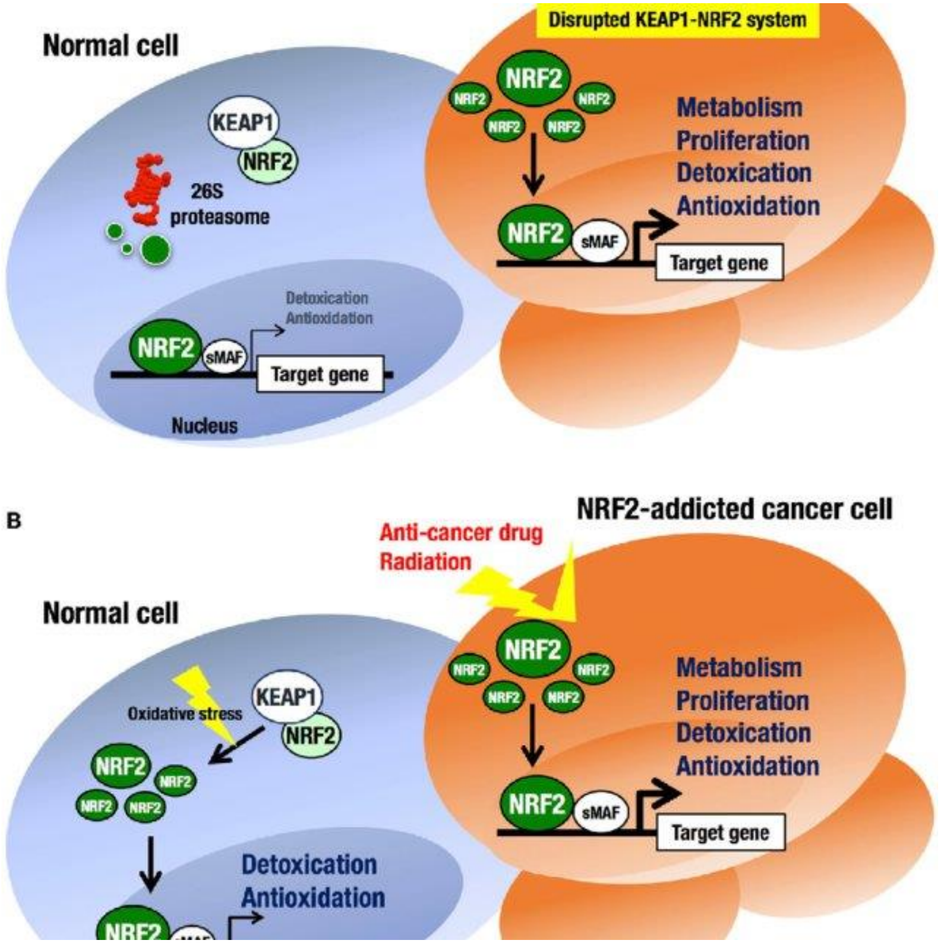
- Nrf2 can protect the liver against Arsenic hepatotoxicity unless overtaxed.
- Nrf2 protects the brain and liver against alcohol consumption, eg protects against acetaminophen toxicity.
- Nrf2 -via SFN improves Th17/Th1-mediated autoimmune disease by inducing HO-1 and inhibiting NF-κB p65-regulated IL-23 and IL-12 expression.

Detailed Nrf2 slides will be after references

YOU CAN READ THEM LATER AS REFERENCES

Lot of info fromhttps://dralexjimenez.com/nrf2-explained-the-keap1-nrf2-pathway/

Nrf2 Overstimulation: too much of a good thing can be BAD



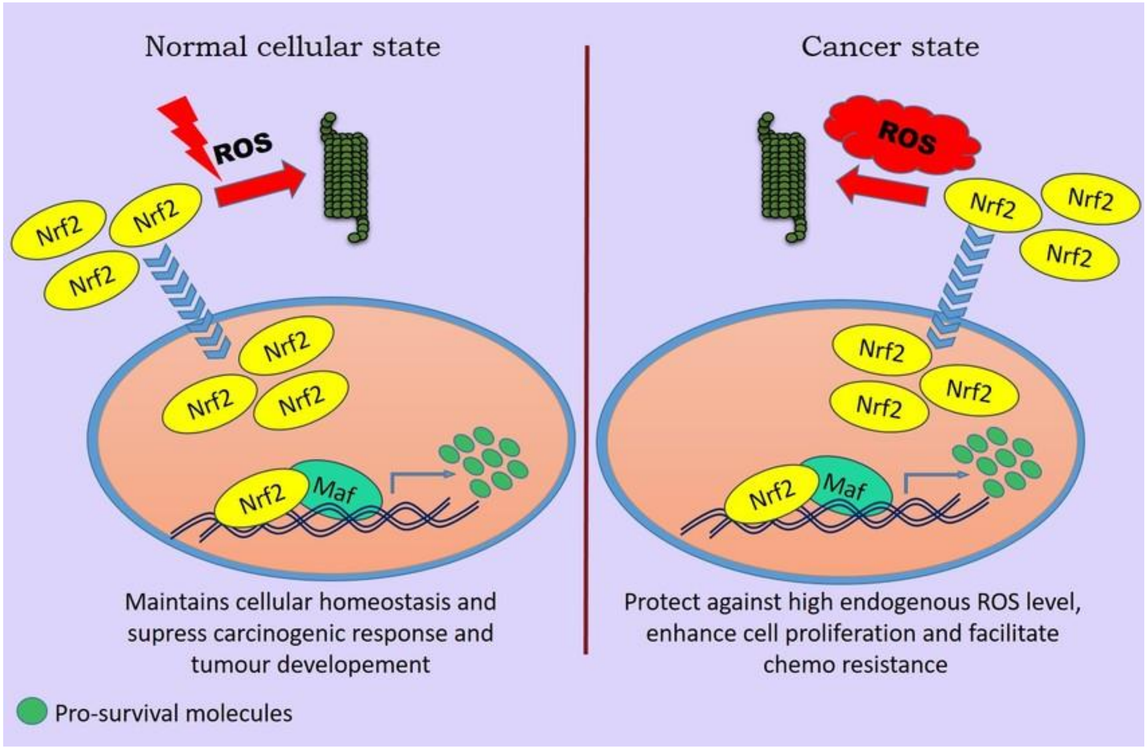
https://www.researchgate.net/figure/Difference-in-NRF2-activation-between-normal-cells-and-NRF2-addicted-cancer-cells-A_fig1_316703001

Some situations require downregulation of Nrf2

Such as in chronic oxidative stress like CIRS , TBI, and cancer…

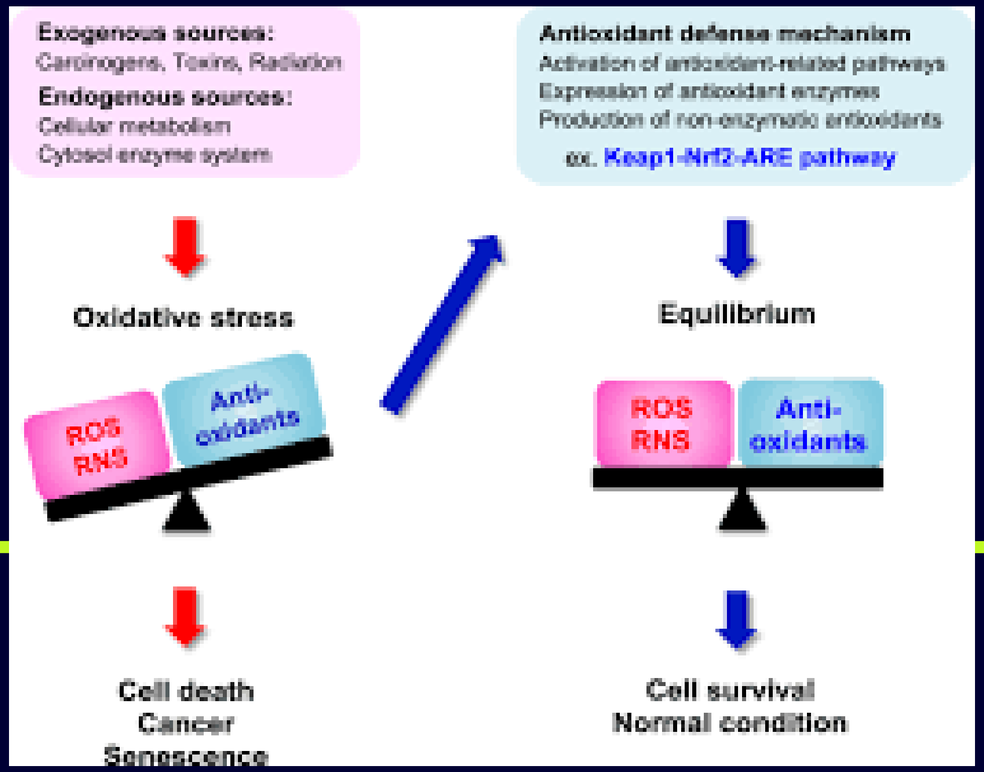
Nrf2 over activation

- Overstimulated /tired Nrf2 system will not protect from inflammation including cancer but promote it .
- Hence delicate balance between intermittent stimulation of Nrf2 and avoiding overstimulation of Nrf2 is crucial in chronic disease states including cancer.
- Some causes for NRF2 overexpression can be genetic mutation especially to Keap1 , continued a chronic exposure to a toxin or oxidative stress. Eg Nrf2 KO mice tend to develop autoimmune diseases and are susceptible to a wide variety of disease conditions including cancer.



https://www.researchgate.net/figure/Schematic-representation-of-the-dual-role-of-Nrf2-in-cancer-progression-and-therapy_fig1_317586485

The key is to stimulate Nrf2 appropriately to help the body



https://link.springer.com/article/10.1007/s00044-020-02539-y

SOME GENERAL WAYS TO INCREASE NRF2

- Exercise + CoQ10(ubiquinol) + Sun (these synergize very well)
- Broccoli Sprouts
- Butyrate +” Super Coffee"(added MCT, Theanine, curcumin,cordiceps, taurine) + Morning Sun
- Acupuncture
- Fasting
- Cannabidiol (CBD)
- Lion's Mane + Melatonin
- Alpha-lipoic acid + DIM
- Wormwood
- PPAR-gamma Activation

- Cold (showers, plunges, ice bath, gear, cryotheraphy) R
- EMFs (low frequency, such as PEMF) /RIFE
- Exercise (Acute exercise like HIIT)
- High Fat Diet /ketogenic (diet)
- High Heat (Sauna)
- Hydrogen Inhalation and Hydrogen Water
- Hyperbaric Oxygen Therapy
- Infrared Therapy (such as Joovv)
- Coffee enema

- Intravenous Vitamin C
- Ozone
- Smoking (not recommended - acutely smoking increase Nrf2, chronically smoking decreases Nrf2.
- Sun (UVB and Infrared)

Foods that increase Nrf2

- Dark chocolate or cacao nibs
- Vegetables–cruciferous vegetables in particular like cauliflower, bok choy, and broccoli microgreens- Broccoli, broccoli sprouts, cabbage, kale, collard greens, cauliflower, bok choy, and Brussels sprouts (sulforaphane)
- Kimchi
- Herbs and spices–especially cloves, ginger, cinnamon, turmeric, yellow mustard, and oregano
- Legumes -soy beans and other soy products; green beans, peanuts
- Red wine–must be red because the grape skin contains most of the antioxidants
- Tea, especially white and green teas
- Garlic and onion (sulfur compounds)
- Grapes, cranberries, blueberries, mulberries, lingonberries, bilberries, jackfruit

Supplements can increase Nrf2 but not all made equal
List of supplements that activate Nrf2 is after the references below

- Not all Nrf2-activating supplements are made equally or ethically and can be expensive .
  Eg ,There are many sulforaphane-based supplements that say they're made from broccoli and don't actually contain any broccoli!
- Just broccoli or cruciferous vegetables (or supplements) may not be enough as many of us may not activate glucoraphanin to sulforaphane . Glucoraphanin is precursor of sulforaphane–you need the enzyme to convert to sulforaphane. This enzyme is myrosinase which is in mustard seeds and greens, radish, watercress, wasabi, daikon (and broccoli itself).
- Similarly, there are some supplements that just contain glucoraphanin–the precursor of sulforaphane–but don't contain the enzyme needed to make the sulforaphane.You need Myrosinase in the same product if possible

Supplements that enhance Nrf2

- **Acetyl-L-Carnitine** (ALCAR) and Carnitine R Allicin
- Alpha-lipoic acid -esp for mitochondria genesis
- Amentoflavone
- Andrographis paniculata
- Agmatine
- **Apigenin**
- **Arginine**
- Artichoke (Cyanropicrin)
- **Ashwaganda**
- **Astragalus**
- **Bacopa**
- Beefsteak (Isogemaketone)
- **Berberine R**
- Beta-caryophyllene
- Bidens Pilosa
- Black Cumin Seed Oil (Thymoquinone)
- Boswellia
- Butein
- **Butyrate**
- **Cannabidiol (CBD)**
- **Carotenioids Beta-carotene (synergy with Lycopene - 2 × 15 mg/d lycopene), Fucoxanthin, Zeaxanthin, Astaxanthin, and Lutein)**
- Chitrak
- **Chlorella**
- **Chlorophyll**
- Chrysanthemum zawadskii
- Cinnamomea
- Common Sundew
- Copper
- **Coptis**
- **CoQ10**
- **Curcumin**
- Damiana

Supplements that enhance Nrf2

- **Dan Shen/Red Sage (Miltirone) esp mitochondria genesis**
- **DIM**
- Dioscin
- Dong Ling Cao
- **Dong Quai** (female ginseng)
- Ecklonia Cava
- **EGCG**
- Elecampane / Inula
- Eucommia Bark
- Ferulic Acid
- Fisetin
- **Fish Oil** (DHA/EPA - 3 × 1 g/d fish oil containing 1098 mg EPA and 549 mg DHA
- **Galangal**
- Gastrodin (Tian Ma)
- Gentiana
- **Geranium**
- **Ginkgo Biloba (Ginkgolide B)**
- **Glasswort**
- **Gotu Kola**
- **Grape Seed Extract**
- Hairy Agrimony
- **Haritaki** (**Triphala**)
- **Hawthorn**
- Helichrysum
- Henna (Juglone)
- Hibiscus
- Higenamine
- **Holy Basil/Tulsi** (Ursolic Acid)
- **Hops**
- **Horny Goat Weed** (Icariin/Icariside)
- Indigo Naturalis
- **Iron** (not recommended unless essential)

Supplements that enhance Nrf2

- **I3C**
- Job's Tears
- **Moringa Oleifera (such as Kaempferol)**
- **Inchinkoto (combo of Zhi Zi and Wormwood)**
- **Kudzu Root**
- **Licorice Root**
- Lindera Root
- **Luteolin (high doses for activation, lower doses inhibit Nrf2 in cancer**
- Magnolia
- Manjistha
- Maximowiczianum (Acerogenin A)
- **Methylene Blue**
- Mexican Arnica
- **Milk Thistle**
- MitoQ
- Mu Xiang
- **Mucuna Pruriens**
- **Nicotinamide and NAD+**
- **Panax Ginseng**
- **Passionflower (such as Chrysin, but chyrisin may also**
- **Pau d'arco (Lapacho)**
- Phloretin
- Piceatannol
- **PQQ**
- **Procyanidin**
- **Pterostilbene**
- Pueraria

Supplements that enhance Nrf2

- **Quercetin (high doses only, lower doses inhibit Nrf2)**
- Qiang Huo
- Red Clover
- **Resveratrol (Piceid and other phytoestrogens essentially, Knotweed)**
- **Rose Hips**
- Rosewood
- **Rutin**
- Sappanwood
- **Sarsaparilla**
- Saururus chinensis
- SC-E1 (Gypsum, Jasmine, Licorice, Kudzu, and Balloon Flower)
- **Schisandra**
- Self Heal (prunella)
- **Skull cap (Baicalin and Wogonin)**
- Sheep Sorrel
- Si Wu Tang
- Sideritis
- Spikenard (Aralia)
- **Spirulina**
- **St. John's Wort**
- **Sulforaphane**
- Sutherlandia
- Tao Hong Si Wu
- **Taurine**
- Thunder God Vine (Triptolide)
- **Tocopherols (such as Vitamin E or Linalool)**
- **Tribulus**
- Tu Si Zi
- **TUDCA -Bile acid**

Supplements that enhance Nrf2

- **Vitamin A (although other retinoids inhibit Nrf2)**
- **Vitamin C (high dose only, low does inhibits Nrf2)**
- **Vitex/Chaste Tree**
- White Peony (Paeoniflorin from Paeonia lactiflora)
- **Wormwood (**Hispidulin and Artemisinin)
- Xiao Yao Wan (Free and Easy Wanderer)
- Yerba Santa (Eriodictyol)
- Yuan Zhi (Tenuigenin)
- Zi Cao (will reduce NRF2 in cancer)
- **Zinc**
- **Ziziphus Jujube**

There is a key nutrient for Nrf2 activation…

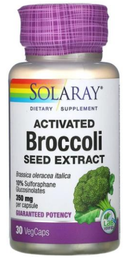
Comparison example supplements

- Dr Mercola Broccoli Sprout Serving Size: 1 Capsule:
Organic Fermented Broccoli Sprout:400 mg
Organic Broccoli:(Whole Plant):100 mg
Glucoraphanin:350 mcg
Sulforaphane:140 mcg(14mg)
Myrosinase :105 mcg

- Source Natural Broccoli Sprout 2 Caps:
Sprouted Broccoli Extract Blend
Yielding 2,000 mcg (20mg) Sulforaphane

- Thorne Crucera -SGS. 1 Caps
(from Broccoli extract (seed) (Brassica oleracea italica)
Sulforaphane Glucosinolate 50 mg

* Enduracell :glucurophanin 40mg - not sulforaphane-still needs Myrosinase



*SolarayBroccoli
Broccoli (Brassica oleracea italica) (seed extract)
(Guaranteed to contain 35 mg [10%] Sulforaphane Glucosinolates and Supplying Myrosinase Enzyme Activity) 350mg

Protandim Nrf2 activator

Does not contain sulfoparane-tumeric, green tea, Bacopa,milk thistle

A broccoli a day can keep doctors away!!!?

Sulforaphane reactivates cellular antioxidant defense by inducing Nrf2/ARE/Prdx6 activity during aging and oxidative stress

- Eri Kubo, Bhavana Chhunchha, Prerna Singh, Hiroshi Sasaki & Dhirendra P. Singh

Scientific Reports

volume

7, Article number: 14130 (2017) Cite this article

Abstract

Upon oxidative stress and aging, Nrf2 (NFE2-related factor2) triggers antioxidant defense genes to defends against homeostatic failure. Using human(h) or rat(r) lens epithelial cells (LECs) and aging human lenses, we showed that a progressive increase in oxidative load during aging was linked to a decline in Prdx6 expression. DNA binding experiments using gel-shift and ChIP assays demonstrated a progressive reduction in Nrf2/ARE binding (−357/−349) of Prdx6 promoter. The promoter (−918) with ARE showed a marked reduction in young vs aged hLECs, which was directly correlated to decreased Nrf2/ARE binding. A Nrf2 activator, Sulforaphane (SFN), augmented Prdx6, catalase and GST*π* expression in dose-dependent fashion, and halted Nrf2 dysregulation of these antioxidants. SFN reinforced Nrf2/DNA binding and increased promoter activities by enhancing expression and facilitating Nrf2 translocalization in nucleus. Conversely, promoter mutated at ARE site did not respond to SFN, validating the SFN-mediated restoration of Nrf2/ARE signaling. Furthermore, SFN rescued cells from UVB-induced toxicity in dose-dependent fashion, which was consistent with SFN’s dose-dependent activation of Nrf2/ARE interaction. Importantly, knockdown of Prdx6 revealed that Prdx6 expression was prerequisite for SFN-mediated cytoprotection. Collectively, our results suggest that loss of Prdx6 caused by dysregulation of ARE/Nrf2 can be attenuated through a SFN, to combat diseases associated with aging.

Sulforaphane

Sulforaphane is an isothiocyanate occurring in stored form as **glucoraphanin** in cruciferous vegetables such as cabbage, cauliflower, and kale, and at high levels in broccoli especially in **broccoli sprouts**. **Glucoraphanin** is the main glucosinolate found in brassicas.

Glucoraphanin requires the plant enzyme **myrosinase** for converting it into **sulforaphane**. **Sulforaphane** is metabolized through mercapturic acid pathway, being conjugated with glutathione and undergoes further biotransformation, yielding metabolites.

It has been shown that **sulforaphane** may protect against various types of cancer, may also decrease the risk of cardiovascular disease, and help in autism and osteoporosis.

Recommended dose widely varies pending on quality of product, the kind of **glucurophanin,** presence of **Myrosinase in the microbiome** and destroyed by heat.

Sulphoraphane

Although an ideal dosage is not known, supplementation of 0.1-0.5mg/kg sulforaphane to rats has been noted to be bioactive. This is an estimated human dose of:

- **7-34 mg for a 68kg person**
- **9-45 mg for a 90kg person**
- **11-57 mg for a 113kg person**

These low quantities are likely attainable via raw broccoli or cruciferious vegetable products, while higher doses may be further beneficial. The optimal supplemental dose of sulforaphane is unknown.

- Researched **sulforphane** is around 50-60mcg, recommend between 50mcg-400mcg(5mg -40mg)
- 1 cup (100g)of **broccoli sprouts** have 1200mg **sulforaphane**
- 1 cup(100g)**mature broccoli** has 170 mg **sulforaphane**
- Still need **myrosinase** enzyme in mustard seeds

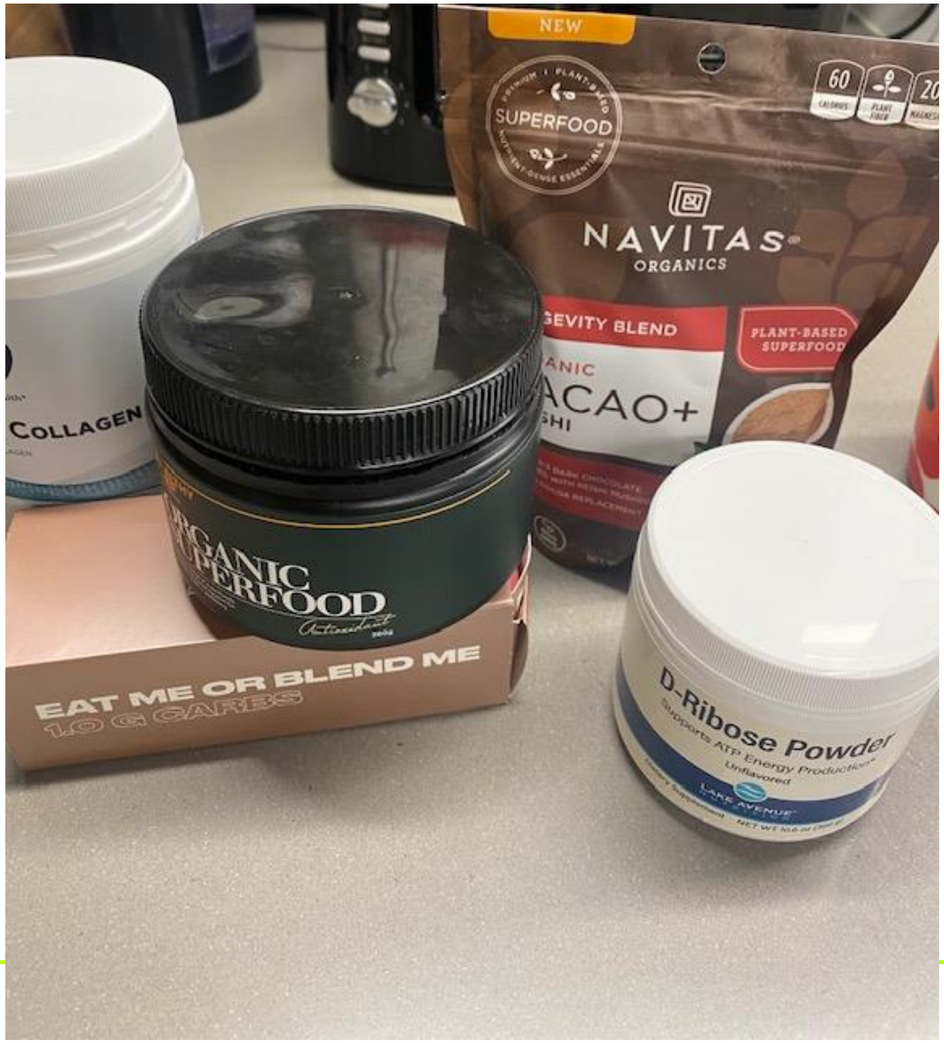
Table 1. Glucosinolate Content of Selected Cruciferous Vegetables

Food (raw)	Serving	Total Glucosinolates (mg)
Brussels sprouts	½ cup (44 g)	104
Garden cress	½ cup (25 g)	98
Mustard greens	½ cup, chopped (28 g)	79
Turnip	½ cup, cubes (65 g)	60
Cabbage, savoy	½ cup, chopped (45 g)	35
Kale	1 cup, chopped (67 g)	67
Watercress	1 cup, chopped (34 g)	32
Kohlrabi	½ cup, chopped (67 g)	31
Cabbage, red	½ cup, chopped (45 g)	29
Broccoli	½ cup, chopped (44 g)	27
Horseradish	1 tablespoon (15 g)	24
Cauliflower	½ cup, chopped (50 g)	22
Bok choy (pak choi)	½ cup, chopped (35 g)	19

Probiotics that increase Nrf2

- Bacillus subtilis
- Clostridium butyricum
- Lactobacillus brevis
- Lactobacillus casei
- Lactobacillus collinoides
- Lactobacillus gasseri
- Lactobacillus helveticus
- Lactobacillus paracasei
- Lactobacillus plantarum
- Lactobacillus rhamnosus

My Nrf2 drink : great for post/ in between exercise



Cacao with cordiceps

D ribose

Collagen

Healthy Chef Organic powder-broccoli sprouts

prebiotic,greens berries B roccoliespouts,

berries

Polyphenols

MCT -fat drop(1/3 of slab is enough

If no cancer add protein powder

TO DECREASE NRF2 IN CHRONIC OXIDATIVE STRESS

Diet, Supplements, And Common Drugs:

- **Apigenin (higher doses)**
- Brucea javanica
- Chestnuts
- **EGCG** (high doses increase Nrf2)
- **Fenugreek** (Trigonelline)
- Hiba (Hinokitiol / β-thujaplicin)
- High Salt Diet
- **Luteolin** (Celery, green pepper, parsley, perilla leaf, and chamomile tea - higher doses may increase Nrf2 - 40 mg/kg luteolin three times per week)
- **Metformin (chronic intake) -that may be one of the reasons Metfromin is useful for cancer patients**
- **N-Acetyl-L-Cysteine** (NAC, by blocking the oxidative response, esp at high doses) >>>liposomal /IV glutathione probably better
- Orange Peel (have polymethoxylated flavonoids)
- **Quercetin** (higher doses may increase Nrf2 - 50 mg/kg/d quercetin) -often used in cancer rx for VEGF in high dose 1-2g
- Salinomycin
- **Retinol** (all-trans retinoic acid)
- **Vitamin C when combined with Quercetin**
- Zi Cao (Purple Gromwel has Shikonin/Alkannin)

Nrf2 and CIRS/Chronic infections

How is it Relevant to our work??

Nrf2 can reduce oxidation, inflammation, enhance detoxification, support mitochondria, reduce MMP9 and TGFB,NF-kB ,mitigate mast cells protect microbiome homeostasis, reduce brain inflammation and mitigate depression and anxiety.

However Nrf2 need to stimulated /suppressed at a suitable amount to help our patients. (Hormetic effect)

That is metered detoxification whilst supporting digestive system and detox pathway , working on limbic system .

CIRS Dx/Rx :

History, history, history

Can present with varying symptoms .Could just be weight issues, cognitive decline, mood decline, metabolic syndrome, autoimmunity, gut, neuro, bladder issues, CFS, ‘fibromyalgia etc

Can they identify the source of mould or need inspection?

Can they afford to have inspection, remediate, move?

air filter /dehimifier possible?

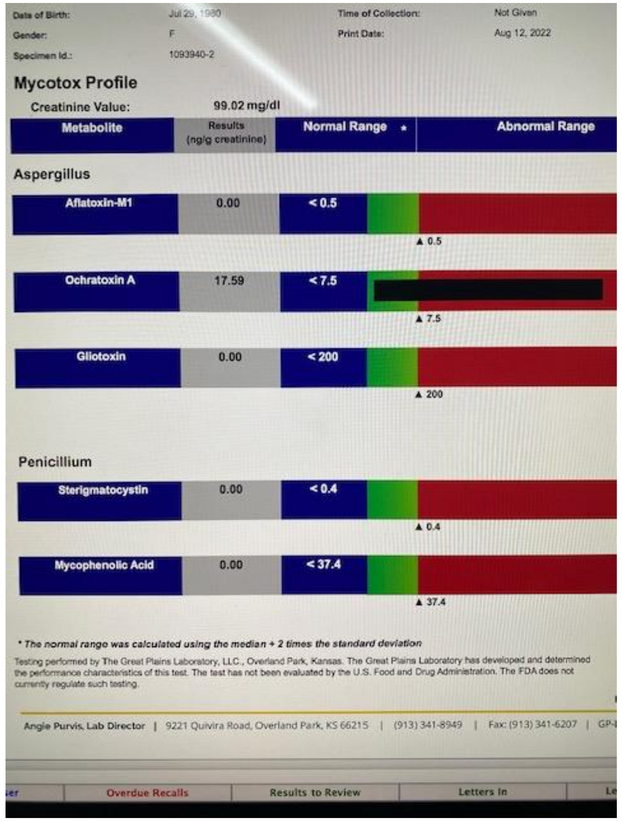
What can be done to minimise exposure?

What is an affordable diagnostic mould test for these patients?

CIRS MAY PRESENT AS….

- MCAS
- Immune dysregulation -chronic infections
- Parasympathetic and Vagus Nerve disruptions
- Methylation dysregulation
- Hormone dysregulation -Estrogen dominace /menopause/andropause
- Low immunity – inability to fight off infections
- Dysbiosis , SIBO/LIBO
- Dysautonomia. eg POTS
- CFS -HPA axis dysregulation
- Sick euthyroid syndrome, hypothyroidism, dysregulated hyperthyroidism
- Cognitive impairment
- Autoimmunity
- Insomnia. Anxiety, depression
- Metabolic syndrome , CVD, stroke
- Histamine/Salicylate/Oxalate issues
- Chronic pain including peripheral neuropathy, exaggerated pain experience ,general pain
- Cancer
- Interstitial cystitis
- Ashma/COPD
- Peripheral neuropathy/MS
- Dementia

URINARY MYCOTOXIN , MYMCOLAB AB, OAT



Date of Birth: Jul 29, 1980 | Time of Collection: Not Given
Gender: F | Print Date: Aug 12, 2022
Specimen Id.: 1093940-2

Mycotox Profile

Creatinine Value: 99.02 mg/dl

Metabolite	Results (ng/g creatinine)	Normal Range *	Abnormal Range
Aspergillus			
Aflatoxin-M1	0.00	< 0.5	▲ 0.5
Ochratoxin A	17.59	< 7.5	▲ 7.5
Gliotoxin	0.00	< 200	▲ 200
Penicillium			
Sterigmatocystin	0.00	< 0.4	▲ 0.4
Mycophenolic Acid	0.00	< 37.4	▲ 37.4

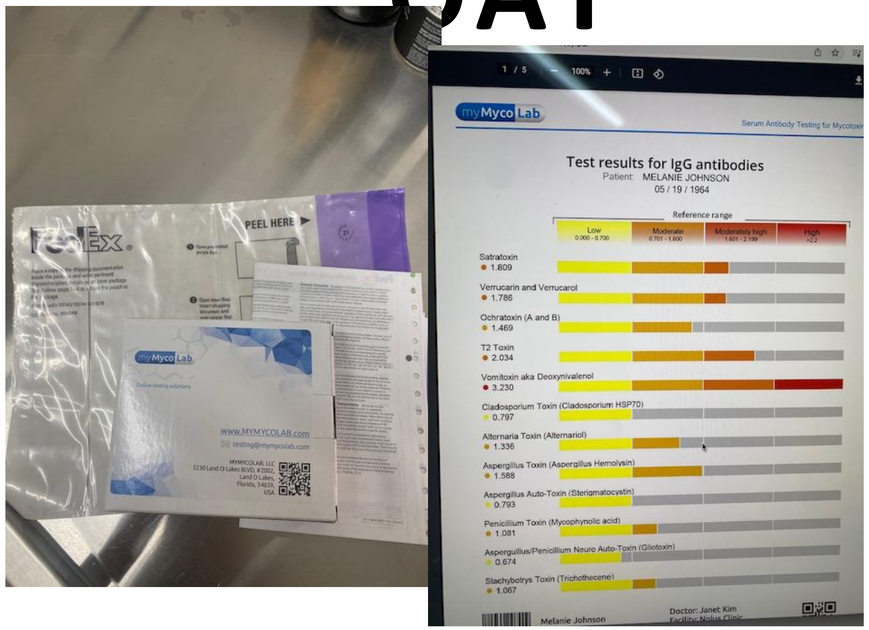
** The normal range was calculated using the median + 2 times the standard deviation*

Testing performed by The Great Plains Laboratory, LLC., Overland Park, Kansas. The Great Plains Laboratory has developed and determined the performance characteristics of this test. The test has not been evaluated by the U.S. Food and Drug Administration. The FDA does not currently regulate such testing.

Angie Purvis, Lab Director | 9221 Quivira Road, Overland Park, KS 66215 | (913) 341-8949 | Fax: (913) 341-6207 | GP-

Overdue Recalls | Results to Review | Letters In

Urinary Mycotoxin
Via GPL (LC), Realtime, lab(Elisa),
Vibrant wellness (microarray)



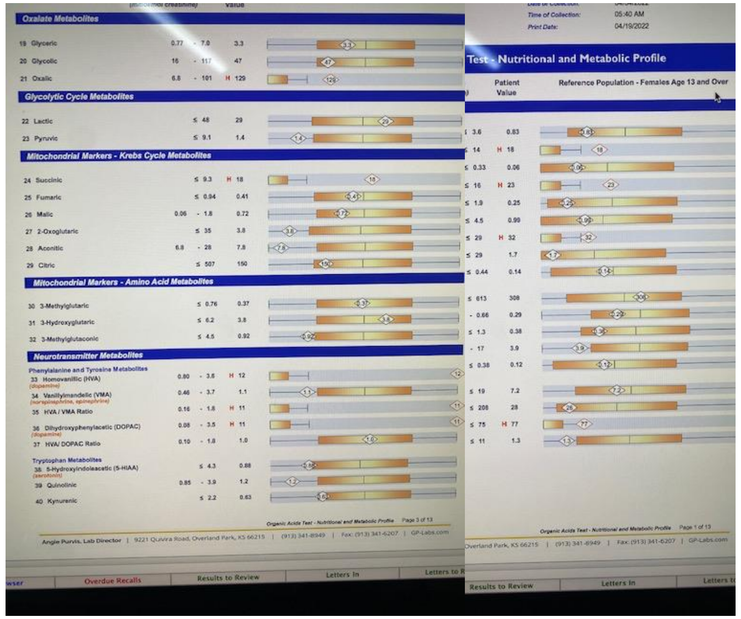
myMycoLab — Serum Antibody Testing for Mycotoxin

Test results for IgG antibodies
Patient: MELANIE JOHNSON
05 / 19 / 1964

Reference range: Low 0.000 - 0.700 | Moderate 0.701 - 1.600 | Moderately high 1.601 - 2.199 | High >2.2

Satratoxin	1.809
Verrucarin and Verrucarol	1.786
Ochratoxin (A and B)	1.469
T2 Toxin	2.034
Vomitoxin aka Deoxynivalenol	3.230
Cladosporium Toxin (Cladosporium HSP70)	0.797
Alternaria Toxin (Alternariol)	1.336
Aspergillus Toxin (Aspergillus Hemolysin)	1.588
Aspergillus Auto-Toxin (Sterigmatocystin)	0.793
Penicillium Toxin (Mycophynolic acid)	1.081
Aspergillus/Penicillium Neuro Auto-Toxin (Gliotoxin)	0.674
Stachybotrys Toxin (Trichothecene)	1.067

Melanie Johnson — Doctor: Janet Kim



Oxalate Metabolites

19 Glyceric	0.77 - 7.0		3.3	
20 Glycolic	16 - 117		47	
21 Oxalic	6.8 - 101	H	129	

Glycolytic Cycle Metabolites

22 Lactic	≤ 48		29	
23 Pyruvic	≤ 9.1		1.4	

Mitochondrial Markers - Krebs Cycle Metabolites

24 Succinic	≤ 9.3	H	18	
25 Fumaric	≤ 0.94		0.41	
26 Malic	0.06 - 1.8		0.72	
27 2-Oxoglutaric	≤ 35		3.8	
28 Aconitic	6.8 - 28		7.8	
29 Citric	≤ 507		150	

Mitochondrial Markers - Amino Acid Metabolites

30 3-Methylglutaric	≤ 0.76		0.37	
31 3-Hydroxyglutaric	≤ 6.2		3.8	
32 3-Methylglutaconic	≤ 4.5		0.92	

Neurotransmitter Metabolites

Phenylalanine and Tyrosine Metabolites

33 Homovanillic (HVA) (dopamine)	0.80 - 3.6	H	12	
34 Vanillylmandelic (VMA) (norepinephrine, epinephrine)	0.46 - 3.7		1.1	
35 HVA / VMA Ratio	0.16 - 1.8	H	11	
36 Dihydroxyphenylacetic (DOPAC) (dopamine)	0.08 - 3.5	H	11	
37 HVA/ DOPAC Ratio	0.10 - 1.8		1.0	

Tryptophan Metabolites

38 5-Hydroxyindoleacetic (5-HIAA) (serotonin)	≤ 4.3		0.88	
39 Quinolinic	0.85 - 3.9		1.2	
40 Kynurenic	≤ 2.2		0.63	

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Overdue Recalls | Results to Review | Letters In

Test - Nutritional and Metabolic Profile

Time of Collection: 05:40 AM
Print Date: 04/19/2022

	Patient Value	Reference Population - Females Age 13 and Over
	3.6	0.83
	14 H	18
	≤ 0.33	0.06
	≤ 16 H	23
	≤ 1.9	0.25
	≤ 4.5	0.90
	≤ 29 H	32
	≤ 29	1.7
	≤ 0.44	0.14
	≤ 613	309
	- 0.66	0.29
	≤ 1.3	0.38
	- 17	3.9
	≤ 0.38	0.12
	≤ 19	7.2
	≤ 208	28
	≤ 75 H	77
	≤ 11	1.3

Organic Acids Test - Nutritional and Metabolic Profile Page 1 of 13

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Results to Review | Letters In

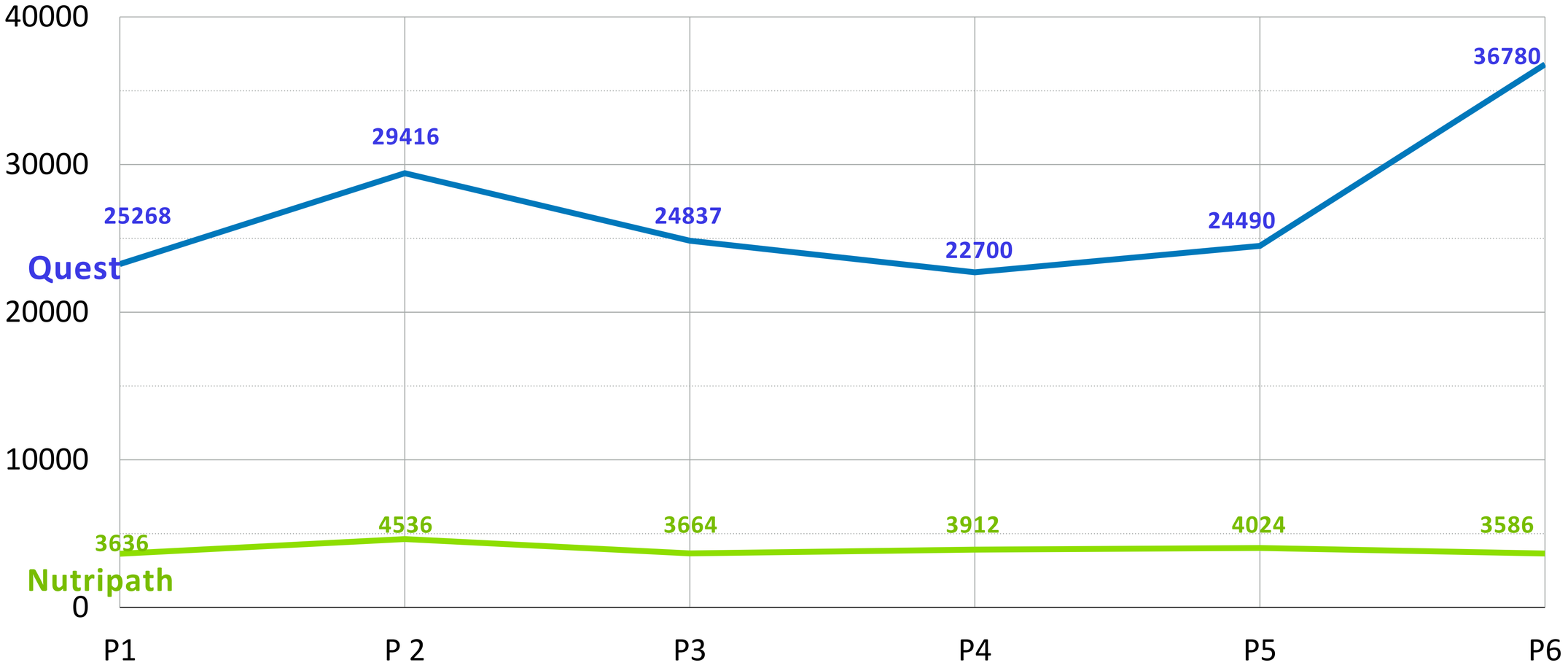
Organic Acids Test via GPL

Aspergilllus,
oxaloglutaric acid
Arabinose ,Tartaric, Tricarballyic,
glyceric acid, glycolic acid, and oxalic acid
pyroglutamic acid

myMycoLab

MyMycoLab
testing@mymycolab.com
(813) 575-7924
Click to visit our website.

22/3/16 collection for Quest and Nutripath -same sample used



OTHER INVESTIGATIONS: SOME CAN BE SPREAD OUT THROUGH SUBSEQUENT CONSULTATIONS- FINANCIAL REASON

- Physical examinations, VCS (mostly pass)
- MC: Basc bloods , FBC, electrolyte, chol, panel , insulin, full iron (for saturation issues),vit Se B12, Vit D, homocysteine, ANA, thyroid ab, Coeliac serology, IGG/IGA/IGM, 24 hr urinary cortisol, am cortisol, ACTH, sex hormones including DHEAs at luteal phase for females and random for males, PSA
- Cd 57? , Cd4/Cd8?(most have Th2 dominance)
- Private: HLA DQDR Coeliac gene test, HLA DQDR gene test , TSH , T4, T3, RT3
- I tend to do VIP later closer to the time they are completing treatment as it is private and expensive, Leptin occasionally.
- CDSA, SIBO pending symptoms as these need treatment before detox
- ECP, tryptase, chromogranin A,If symptomatic of MCAS
- Aspergillus IGG?
- MARCoNs can be done further down the track as again costs too much up front
- NQ if suspect neurological issues. Eg, memory, trauma, apathy, depression
- Heavy metals not done early as does not show true levels too early. Can be done later

MAIN TREATMENTS

- If present and too affected can use ‘rescue remedy’ HCG injection for 3-6 weeks whilst organising their lives
- Treat SIBO/LIBO. Clean up diet
- Start Glutathione liposomal early. Support thyroid early
- Start digestive enzymes eg Bio-Gest and Super enzymes with each meal- helps GB and reduces reflux, mitigate SIBO, feeds healthy biome
- After 2 weeks of low amylose diet with high dose fish oil (2.4 gm EPA and 1.8 gm DHA). start CSM(qid)/Colesevelam2bd or tds/Questran (qid) . Between meals for CSM and Questran. But Colesevelam can be with food but if taking supplements on empty stomach
- Duration determined by history, repeat mould test if affordable.
- MARCoNS treated couple of courses into CSM/Colesevelam/Questran. Too early can result in being on the nasal spray too long. (EDTA 1-2% +silver nasal spray +_ Mucolox and Amphotericin) Usually require 3 -6 courses.
- HCG used again for reduction of inflammation
- VIP nasal spray -approx 6 months -50mcg alternating nostril x4/day- doses nay need to vary pending response /reaction- check lipase 2 weeks into rx then every 3 months . Check BP when initiate . If lipase rises can do small doses or sometimes need to stop

BINDERS

- CSM/Questran/Colesevelam: works by directly binding bile in the GI tract. This causes a reduced bile resorption and an increased conversion of cholesterol to bile, via 7a-hydroxylation, thus lowering cholesterol levels. In this process toxin laden bile is bound and thus excreted via stool. Binds to all esp OTA.
- Clay(bentonite/zeolite) :Aflatoxin. Zearalenone, OTA,gliotoxin but nutrients too
- Charcoal : OTA ,aflatoxins, tricothecenes. and nutrients
- Glucomannan: Aftatoxin, OTA, zearalenone
- Chlorella : esp useful for pregnant women :heavy metals and Aflatoxin
- Humic/Fulvic acid: antiinflammatory and general toxin binders
- Zeolite: binds to Histmines,…….Enterosgel(silica) also binds to histamine, al,
- Pair up with glutathione (liposomal/NAC)
- Probiotics: L. pentosus and L. beveris. L. plantarum C88. bind to aflatoxins, but it also works by upregulating the antioxidant activity of GST. It also sterigmatocystin.
  Sac Boulardii binds to zearalenone, enniatin b, OTA, gliotoxin, and aflatoxins:
  https://youarethehealer.org/mold-and-toxins/moldy-people/healing-from-mold/types-of-toxin-mycotoxin-binders/probiotics-to-biotransform-toxins/

BINDER DOSES

- CSM compounded /Questran 4g qid on empty stomach- stay away from thyroid med at least 2-4 hrs
- Colesevelam 625mg 2bd /tds before food or empty stomach .Can be with food if provide digestive enzymes with bile and not on supplements - stay away from thyroid med 2 hrs
- Natural binders : Ultrabinder/Gi detox (combined charcoal/clay/zeolite/fulvic acid) 1tsp bd on empty stomach and 2 bd on empty stomach
- Chlorella 500mg-1g once to 3 times a day on empty stomach
- Fiber eg Glucomannan eg Optifiber Xymogen: before bed would be best -some people cannot tolerate this at all.
- Sacc boulardii with meals once a day

MYCOTOXINS AND THEIR PHYSIOLOGICAL EFFECT

MYCOTOXINS/Labs	PRODUCING ORGANISM	EFFECT	OTHER COMMENTS	DETOX BY
Aflatoxins(B.G,M) esp AFM1=metabolite of Aflatoxin B1 GPL/RTL	Aspergillus Penicillium	Nephrotoxic, Inhibit leukocytes, Carcinogenic,Nephr-otoxic,Neurotoxic Lung Aspergillus, heamorrhage,coma, death Worse if combined with Ochroatoxin &Zearalenone	In decaying beans, corn, rice, tree nuts, wheat, milk, eggs, and meat. Aflatoxicosis are non-pruritic macular rash, headache, gastrointestinal dysfunction (often extreme), lower extremity edema, anemia, and jaundice.	CSM/Colesevelam Bentonite clay Zeolite.Activated Charcoal Sacc Boulardii Chlorella Fiber(eg Glucomannan)
Trichothescenes GPL(Roridin,Verrucarin)/RTL	All Trichothescenes are lipophyillic and hydrphyllic Macrocyclic trichothecene Fusarium,Stachybotrys	Cytotoxic Immunotoxic, neurotoxic, CVS, indocrine disruptors, dermatotoxcic haemorragic,(spleen), GIT(gastric)	Airbone(WDB) Poisonous mushromms in Japan, China Contaminated vegetation e.g. spinach and grains	CSM/Colesevelam Activated Charcoal Chlorella, Bentonite clay L Rhamnosus Fiber eg Glucomannan
Trichothescenes -Setratoxin G H F	Stachybotrys	Immunoloxic	Airbone(WDB),	as above
Trichothescenes -Roridin E,H,L	Macrocyclic trichothecene Fusarium,Stachybotrys	Immunotoxic, neurotoxic, CVS,GIT Endocrine disruptors	Airbone(WDB) Contaminated vegetation e.g. spinach	as above
Trichothescenes	Stchybotrys,	Immunotoxic,	Airborne(WDB)	CSM/Colesevelam

MYCOTOXINS AND THEIR PHYSIOLOGICAL EFFECT

MYCOTOXINS/Labs	PRODUCING ORGANISM	EFFECT	OTHER COMMENTS	DETOX BY
Enniatin B GPL	Fusarium	Toxic to bone AcetylCoA,Hepatotoxic,Nephrotoxic	Airbone(WDB), Cereal contaminants grains	CSM/Colesevelam Bentonite clay Activated charcoal Chlorella
Citrinin GPL	Aspergillus, Penicillium Monascus.	Nephrotoxic Hepatotoxic Carcinogenic	Airbone(WDB) stored grains, fruits and other plant products	CSM/Colesevelam Activated charcoal Sacc Boulardii Oregano oil
-Dihydrocit-rinone GPL	metabolite of Citrinin (CTN)-Aspergillus Penicillum, Monascus	Carcinogenic, Immunotoxic, Nephrotoxic, toxic to Mitochondria	Airbone(WDB), Ingestion, skin contact irritation	CSM/Colesevelam
Zearalenone GPL	Fusarium	Estrogenic,Carcinogenic (esp Breast) Teratogenic, Immunotoxic, Hepatotoxic	Airbone(WDB) maize, wheat,barley rice from Europe Africa,Asia, impairs lymphocyte response	CSM/Colesevelam Bentonite Clay , Sacch Boulardii, Lactobacillus, Bacillus Licheniformia Chlorella
OCHRATOXIN GPL/RTL	Aspergillus, Penicillium	Carcinogenic Nephrotoxic, Hepatotoxic Teratogenic	Airbone(WDB) graines,grape juice, cereals, wines,dairy, spices,spices	CSM/Colesevelam Activated charcoal, Zeolite also can sweat out,
Gliotoxin GPL/RTL	Aspergillus, Penicilium	Immunotoxic, carcinogenic, Neurotoxic,lungs	Airborne(WDB). can irritate skin,eyes,lymphoma,mammary tumours	CSM/Colesevelam Bentonite clay, Sacc Boulardii, NAC/glutathione/Nystatin

MYCOTOXINS AND THEIR PHYSIOLOGICAL EFFECT

MYCOTOXINS/ Labs	PRODUCING ORGANISM	EFFECT	OTHER COMMENTS	DETOX BY
Mycophnolic Acid GPL	Aspergillus Penicilium	Immunosuppressant to T ,B lymphocytes, carcinogenic,Neurotoxic, damages lungs, cause miscarriage, teratogenic, increase candida and clostridium infections	Airbone(WDB) grains,	CSM/Colesevelam Glutathione Activated charcoal
Sterigomatocyst-in(STG) GPL	Aspergillus Penicillum, Bipolaris	Hepatotoxic, Nephrotoxic, Immunotoxic. Toxic to GI tract	damp carpet dust found in corn, bread cheese, legumes coffee,grains,	CSM/Colesevelam BentoniteClay,Zeolite, Activated charcoal, Sacc Boulardii Chlorella
Chaetoglobosin A GPL	Chaetomium globosum	Neurotoxic, Peritonitis, Cutaneous	Airbone(WDB), plants, soil, straw	+CSM/Colesevelam Phenylalanine, Vit A E, C NAC help
Patulin GPL	Penicillium Aspergillus	Carcinogenic Immunotoxic, Genetoxic	Airborne, decaying apples, fruits	As above and also can sweat out
Fumosinin GPL	Fusartium, Alternaria	Carcinogenic, Hepatotoxic	Airbone(WDB), Corn,cotton,grain dust	CSM/Colesevelam Bentonite Clay/Zeolite

Neuroquant

Neuroquant is a volumetric imaging is an MRI of the brain with computerised ananlaysis of multiple grey and white matter regions. In essense it takes 2D segnmented images and reconstructs their 3D volumes.

Neuroquant is also used as an assesment of environemtally acquired neuroinflammation using volumetric imaging. The brain is greatly affected by inhalational toxicity, trauma and infections. More than half the symptoms commonly seen are neurological cognitive or psychiatric.

Neuroinflammation, microglial activation can lead to neurodegeneration. Hence the neuroquant is a useful tool for assesing neuroinfloammation and neurodegeneration.

In TBAR(Triage Brain Atrophy Report)

Values in white shading indicate that the reported value

- falls between the 5th - 95th percentile for normative data of healthy individuals
- average of a healthy population is 50th percentile

Values in red shading indicate that the reported value =atrophy

- brain tissue: less than the 5th percentile for normative data of healthy individuals
- CSF/ventricles: greater than the 95th percentile for normative data of healthy individuals

Values in blue shading indicate that the reported value=hypertrophy

- brain tissue: greater than the 95th percentile for normative data of healthy individuals
- CSF/ventricles: less than the 5th percentile for normative data of healthy individuals

Neuroquant

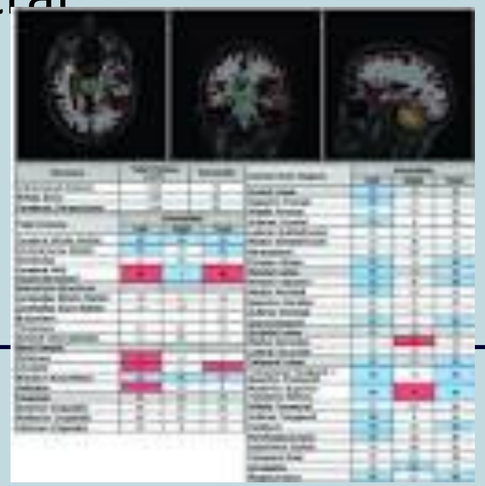
Significant findings CIRS Vs Controls

Hypertrophy (enlargement) of:

Amygdala Thalamus
Post Cingulate Pallidum
Iisthmus Cingulate

Atrophy (shrinkage) of:

Medial parietal ,Paracentral



Significant findigs of Alzhemiers

Prodromal (the early stage and symptoms of any condition)Atrophy of :

Hippocampus
Entorhinal
Pareietal
Post cingulate
Amygdala

Possible asymptomatic - atrophy of :

Prefrontal ,Occipital,Temporal, Parahippocampal

Intracranial Volume (ICV) (cm³)	ICV Percentile
1790.89	74

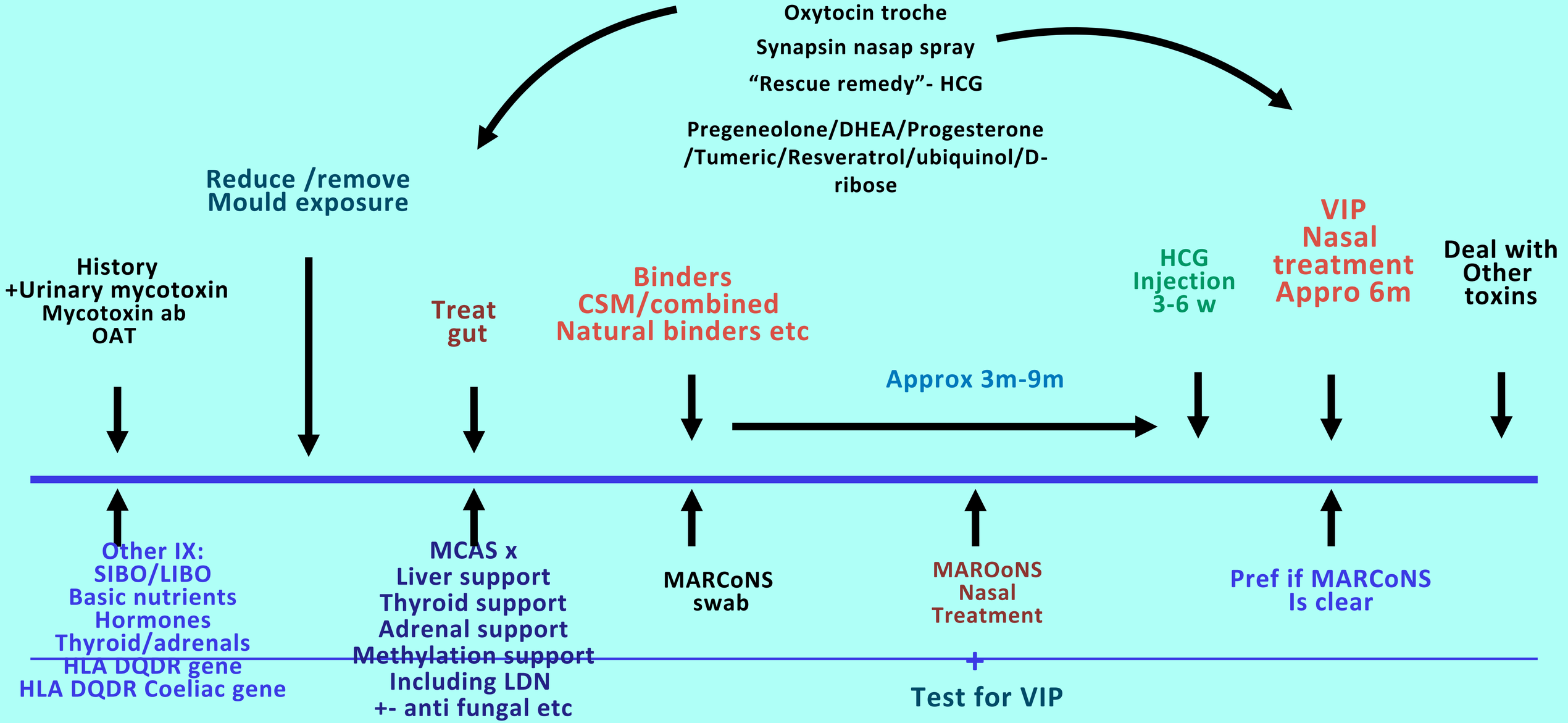
Total Volumes	Percentiles		
	Left	Right	Total
Cerebral White Matter	75	88	82
Cortical Gray Matter	10	11	11
Ventricles	34	43	38
Subcortical Structures			
Cerebellar White Matter	93	87	91
Cerebellar Gray Matter	1	1	1
Brainstem	-	-	1
Thalamus	8	6	6
Ventral Diencephalon	17	27	21
Basal Ganglia			
Putamen	12	25	17
Caudate	9	17	12
Nucleus Accumbens	1	8	1
Pallidum	2	4	2
Cingulate	6	13	8
Anterior Cingulate	26	6	10
Posterior Cingulate	10	30	17
Isthmus Cingulate	13	58	29

Cortical Brain Regions	Percentiles		
	Left	Right	Total
Frontal Lobes	11	14	12
Superior Frontal	16	8	11
Middle Frontal	35	81	61
Inferior Frontal	56	21	37
Lateral Orbitofrontal	12	10	10
Medial Orbitofrontal	14	9	9
Paracentral	1	18	3
Primary Motor	9	27	13
Parietal Lobes	43	26	34
Primary Sensory	31	21	24
Medial Parietal	58	36	48
Superior Parietal	25	4	9
Inferior Parietal	83	85	88
Supramarginal	32	27	26
Occipital Lobes	19	39	26
Medial Occipital	41	25	32
Lateral Occipital	18	57	31
Temporal Lobes	2	2	2
Transverse Temporal + Superior Temporal	9	20	12
Posterior Superior Temporal Sulcus	42	42	42
Middle Temporal	6	8	6
Inferior Temporal	22	21	18
Fusiform	12	1	2
Parahippocampal	1	9	2
Entorhinal Cortex	40	33	33
Temporal Pole	2	5	2
Amygdala	11	5	7
Hippocampus	3	5	3

OTHER USEFUL TREATMENTS

- T3 /thyroid support!!
- LDN - immune, autoimmune, adrenal support, calms brain down increases endorphins
- Pregnenolone 50mg average - immune ,hormone support, calms NMDA receptor, increases cognition removes ammonia from brain, transforms into Cortisol and sex hormones
- DHEAs-keto is what I prefer- safer- helps androgens in particular as Testosterone becomes aromised into oestrogen in CIRS
- For female vaginal estriol and oral micronised progesterone
- Progesterone micronised for estrogen dominance, antianxiolytic, supports T4>>T3
- Synapsin nasal spray for cognitive support
- Oxytocin troche 20-40iu for poor sex drive/IC
- Sodium cromoglycate/ketotifen for MCAS
- Melatonin /liposmal Gaba and Theanine/Cannbis oil
- Oral/intranasal anti -fungal /IV?: (herbs eg Horopito, Caprylic acid etc) or anti fungal med
- Curcumin, Valsartan,Cannabis,Resveratrol,HCG—C4a, MMP9
- Baicalin/skullcap (Scutellaria baicalensis root). HCG, omega 3-VEGF
- Ubiquinol -C3a-statins not necessary

JK's CIRS "modified" flow chart Rx



SHOEMAKER PYRAMID

Perfect storm scenario

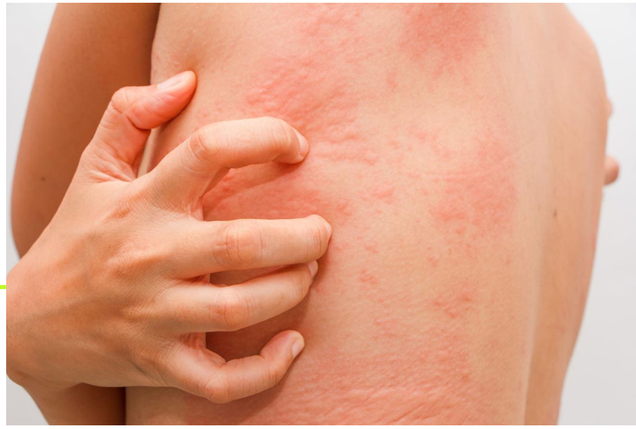
JANET KIM NOV 2022

Perfect Storm: Typical patients

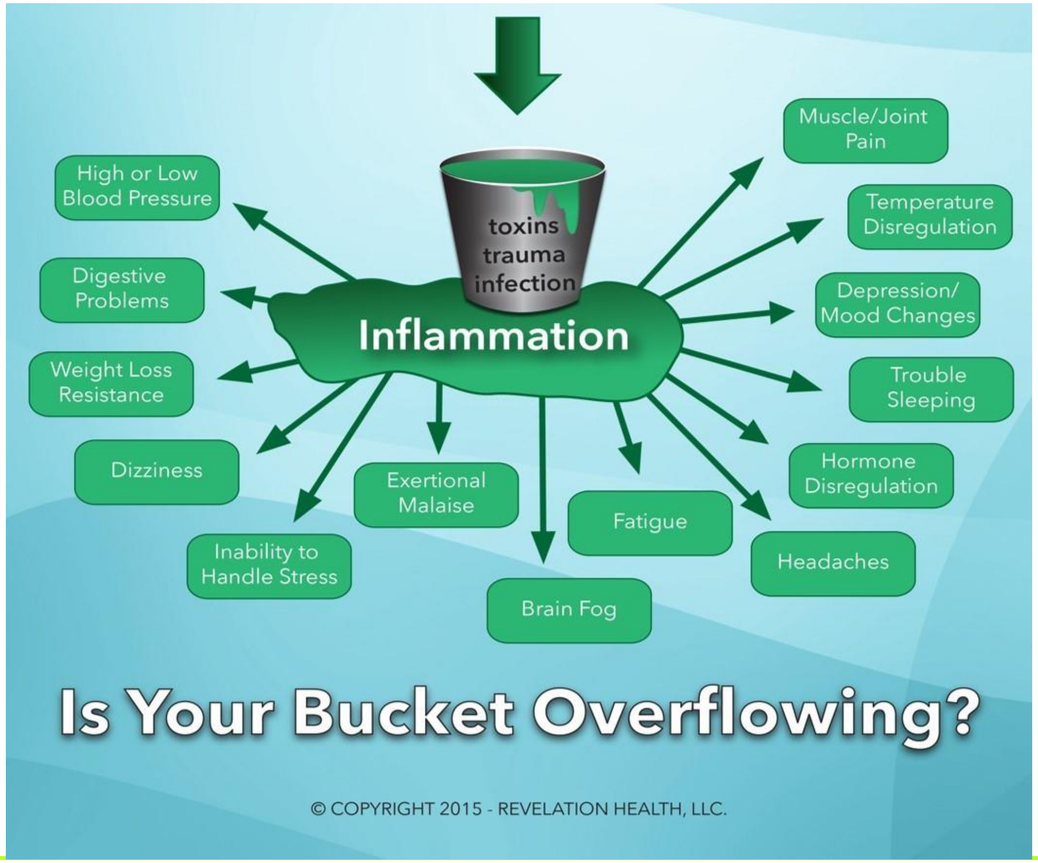
- Patients partially treated for CIRS already on CSM /binders with positive initial response but now feel worse. Have had TBD treated or still in the process.oral or IV antiobiotics , but Disulfiram made worse(-acetyl Aldehyde /molybdenum issue)
- Sometimes no obvious re-exposure to mould elucidated, lives in a safe environment, or still in mouldy /swampy home
- Compliant to supplement regime, take CSM/Colesevelam/other binders, NAC/ glutathione (in addition to other basic active Bs, zinc, mg, D etc)and feels worse or was initially feeling better but now worse after starting binders.
- Does have mouth full of mercury and in the process of replacing with porcelain. Has had root canals and gingivitis.
- Has sinus issues -likely to be MARCoNs and persistent dairy fan.
- Diet is limited , avoids gluten mostly but frequent Asian takeaway. ‘Asian food is healthy-‘
- Experiences bloating and constipation and diarrhoea(has untreated SIBO/LIBO/Parasites.

Perfect storm :Typical patients

- Has Fibromyalgia, MCS(at times EHS), fatigue, cognitive decline, and MCAS symptoms, undermethylating , Pyrrole, MTHFR pos , dysautonomia . Some are hypermobile
- Emotional trauma from the past and illness ..receiving therapy.
- Sensitive to many foods. Oxalates, salicylates, histamines…
- recurrent sterile UTI symptoms -still frequent rx with antibiotics
- Brought many tests from previous doctors including genetic study including unexpressed Coeliac gene, OAT, urinary mycotoxin, Nutripath mould panel etc
- Felt worse during the bush fires (-burnt mouldy houses/trees) and recent rain



How do we reduce toxicity burden in these sensitive patients?



Perfect storm: what's going on

- Unresolved **TBI** overburdened immune antioxidant system,
- **Other toxins** such as GMO gluten and dairy(both also have zonulin) , glyophosate, plastics, heavy metals, mould ,organophapghates, PFOA, and other toxins add to the burden
- **Toxins are drained from ECM-**blood and tissues, dysbiotic gut flora ,root canals, gum and teeth infections, chronic sinusitis and urinary infections, etc result in introducing **Endotoxins/LPS** into the cell wall fragments and enter into the blood and stimulate further inflammatory response, add to the toxicity burden , worse in the presence of gut hyper permeability, (exacerbated by low MSH in CIRS patients).
- All of these issues may result in trauma and dysautonomia resulting in viscous cycle.
- These patient have **high toxicity burden** which **depleted antioxidant reserve** also required to mitigate any further inflammation. Therefore **detoxification capacity is low.**
- **Gall bladder is overwhelemed , leading to choleasthasis.** When bile flow is blocked , it can lead to a buildup of bilirubin and toxins.

Perfect Storm: What's going on

- CIRS, chronic infections, dysbiosis , SIBO, LIBO, heavy metal toxicity all **shut down Nrf2 (mould disables Nrf2 and GSH synthesis** via GCLC-Glutamate-Cysteine Ligase Catalytic Subunit , the first rate-limiting enzyme of glutathione synthesis, and **obstruct phase 2 liver detoxification by 60%**.
- Oxidative stress remain in cells causing **ongoing cell damage** and illness rather than oxidative stress turning Nrf2 into an antioxidant.
- When toxins that are not eliminated by the liver are then **shunted over to the kidneys via the Mrp3** pathway which can **overload the kidneys. Mercury** in combination with **endotoxins,** damage **proximal tubules in the kidneys** further reduce detoxification capacity.
- **Between weakened Nrf2 and depleted GSH** , other toxins are stuck in the cells, potentially leading to a multitude of symptoms. **Stuck in the loop**. Natural detox process is not working.
- While treating this sort of chronic illness/CIRS, **metered discharge of toxins** into the bile will help the **hormetic response** of **Nrf2 activation** to help **GSH synthesis**.

GLUCURONIDATION

- **Nrf2** is involved in **glucuronidation** via inducing **glucuronidation enzymes** UGT1A1 and UGT1A6.
- **Glucuronidation** makes substances water soluble to to be excreted.
- **Nrf2** is involved in **bile acid glucuronidation(=conjugation)** which is one of the many crucial detoxification mechanisms of the human body. **< > Higher levels of unconjugated bilirubin** result in **poor Nrf2 activity**
- **Glucuronidation** is also involved in drug metabolism of substances like drugs,pollutants,androgens, estrogens, mineralocorticoids, glucocorticoids, fatty acid derivatives, retinoids
- **Glucuronidation** is also involved in **mould detoxification (-therefore Oxalates indirectly) ,and break down of salicylates.**
- **Cal d glucarate , Glycine** are useful for **glucuronidation**
- **Unconjugated bile are Toxic bile** (due to insolubility) cause inappropriate **Nrf2 response** >>>**esophagitis, SIBO**>>> rise in **histamine(>>MCAS) salicylates in CIRS**

ABOUT BILE ACIDS

- **Conjugated(or glucuronidated) bilirubin** is **not** reabsorbed from the proximal intestine
- **unconjugated(Non glucuronidated) bilirubin** is partially reabsorbed across the lipid membrane of the small intestinal epithelium and undergoes **enterohepatic circulation. This leads to resorption of toxins.**
- **Conjugation of bile acids** is dependent on the action of **microbiota** in the intestine. AND **vice versa**
- **Conjugation of bile acids** are important in the maintenance of the **microbiota homeostasis and the balance of the mucosal immune system in the intestine, integrity of epithelium of intestine .**
- **If the bile remains toxic and it's not excreted from the human body, it will repeatedly reactivate Nrf2's oxidative stress and eventually turn Nrf2 off and cause patients to feel worse whilst toxins, endotoxins are reabsorbed from the gastrointestinal, or sinus and mouth etc.**

DYSAUTONOMIA,BILE,SIBO,MCAS

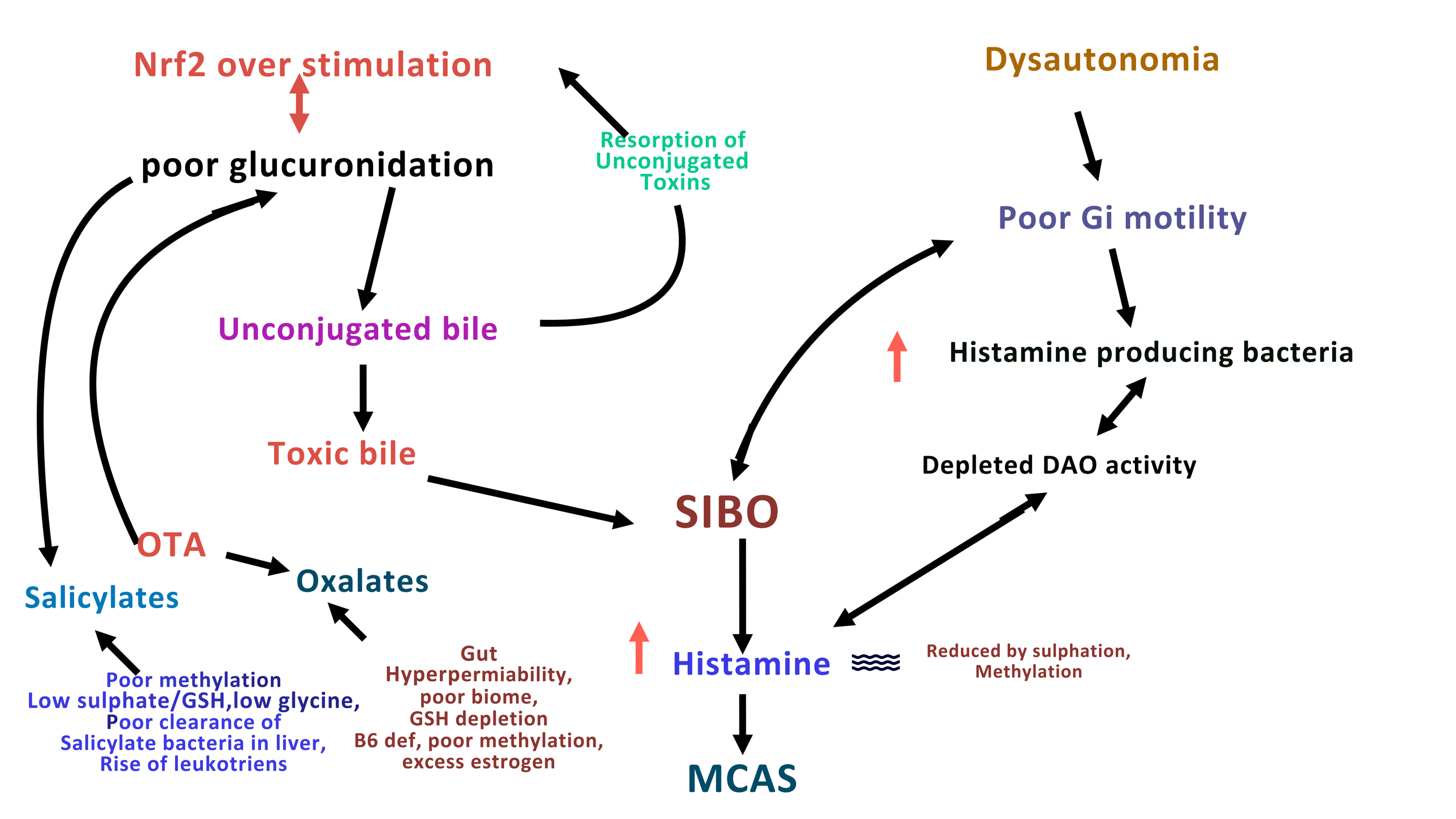
- **Dysautonomia/Dysbiosis** result in SI motility issues, dysbiotic gut flora proliferation,>>>**SIBO**>>> **Histamine** release >>**MCAS** because **DAO enzyme** in the SI **overloaded** with histamine and can't get rid of it all,
- **SIBO impairs DAO activity** and leads to further deficit in DAO, causing ongoing **MCAS** exacerbation
- **SIBO causes over production of not only histamines but also leukotriens, and also overburdens** liver's capacity to clear **Salicylate** producing bacteria leading to **Salicylates sensitivity**
- **Coffee enema (CE)** could be helpful but **CE** can make SIBO patients **more sick as excess toxins are released into inflamed SI.** Gentle binders might help/CE suppositories etc better for this
- **Without addressing SIBO first (And LIBO) patients will struggle to detox.**
- **May use topical** Sodium Cromoglycate 100-200 mg SR oral/cream, ketotifen, ??Quercetin, PEA for MCAS(remember quercetin is a phenol hence can cause salicylate issues in some)

BILIRUBIN AS AN ANTIOXIDANT

- **Biliverdin/bilirubin** can mediate some of **HO-1 antiatherogenic effects.** Exogenous administration of biliverdin, which is promptly converted to bilirubin, appears to be effective in inhibiting atherogenesis in ApoE null mice
- **Serum bilirubin concentrations are inversely correlated with the severity of atherosclerosis in men** . Individuals with “Gilbert syndrome”, characterized by increased levels of circulating unconjugated bilirubin due to a low reactivity of the bilirubin-uridine diphosphate glucuronyl transferase (bilirubin-UGT) enzyme, exhibit a marked reduction in CHD risk
- Health benefit appears likely to stem largely from the fact that physiological intracellular levels of **unconjugated bilirubin inhibit certain common isoforms of NADPH oxidase(and hence preventing ROS).**
- **Hgher plasma bilirubin levels are associated with better insulin sensitivity** and decreased risk for metabolic syndrome and type 2 diabetes—independent of BMI.
- Importance of Bile on gut microbiome discussed previously

OTA/OXALATES

- **Ochratoxin** (OTA)found to cause increase in **oxalates -** one of the reasons why CIRS patients have oxalate issues- may see in OAT test with Aspergillosis mycotoxin, oxalates
- **Oxalates may not break down** due to methylation issues ,def in B6, and when excess oestrogen.
- Gut **hyperpermeability increase oxalate absorption increasing oxalates**
- **OTA particularly block Nrf2**. . **OTA lowers production of GSH** through blocking the two proteins, GCLC(glutamate cysteine ligase) and GCLM(GCL modifier subunit) , **blocks the utilization of existing GSH by lowering levels of GST's.**
- **GSH depletion** increases the **retention of calcium oxalate** in renal cells..
- **B6, Antioxidant therapy (Vit E , NADPH)**might prevent calcium oxalate and kidney stone formation by preventing **oxalate-mediated peroxidative injury** and re-establishing **GSH redox imbalance.**
- Using **Mg Cal citrate** with oxalate foods can bind to oxalates
- **Lactobacilli , Bifidobacteria ,Oxalobacter formigenes** (Creative Biolabs) **probiotics, Biotin** (cofactor for decarboxylate) help breakdown oxalates.
- Oxalate test can also be done by 24 hr urinary oxalate- cheaper for the patient


Nrf2 over stimulation
poor glucuronidation
Resorption of Unconjugated Toxins
Dysautonomia
Poor Gi motility
Unconjugated bile
Histamine producing bacteria
Toxic bile
Depleted DAO activity
SIBO
OTA
Oxalates
Salicylates
Histamine
Reduced by sulphation, Methylation
Poor methylation
Low sulphate/GSH,low glycine,
Poor clearance of
Salicylate bacteria in liver,
Rise of leukotriens
Gut
Hyperpermiability,
poor biome,
GSH depletion
B6 def, poor methylation,
excess estrogen
MCAS

TIPS FOR PERSISTENT SIBO

- Besides Biphasic diet or Fodmaps/Gaps diet, Rifaximin, herbs such as Neem plus. Allimax ,SIBOgurad etc,
- Use Digestive enzymes containing Bile,+-Ursofork(cheaper than Tudca)+ Pancreatic enzymes, and Betaine HCL before each meal.
- In addition, get them to drink a mixture of **apple cider vinegar+ lemon +water** when they take the digestive enzymes just before meals . Boiled ginger water can be used as well
- Get them to **peel ginger and cut them to tiny pieces** (tablet size) and swallow between meals.
- This has been the most successful for intractable SIBO treatment - more effective than repeated antibiotics and protracted herbs.
- **Intermittent fasting** is also helpful as it gives the gut a rest.
- Prokinetic eg Procalopride may help, Gargling helps.
- Glutamine, slippery elm ,fibre not suitable for these patients

+

BTW GARGLING UNTIL YOU TEAR UP…

Dysautonomia causing motility issue can be helped by gargling until tear up.

Gargling stimulates 5th, 9th and 10th cranial nerve and helps with motility issue.

Gargling opens up pharynx and Tg nerve is stimulated promoting digestive system- Gargle at night until tear up.

Push the water or oil back as far back in the throat as you can, and start your gargling there. Need to feel like to gag and that is the point. Gagging, while unpleasant, is another good way to stimulate the vagus nerve.

OTHER FACTORS TO CONSIDER

- Fungal infection in addition to toxicity can be present and may need rx via herbs or antifungals (which are toxic to the liver). Consider **molybdenum** for mitigation of acetyl aldehyde if treating this(>>>acetic acid/acetyl CoA)
- Support their **thyroid , especially T3** as liver toxicity increases **RT3** no matter what TSH, T4, T3 levels show. More CE can help but this depends on the patients . Add T3 even temporarily otherwise their adrenals may not pick up. Adrenal function needs robust thyroid function to support the patients
- **Ozone and oxygen therapies** , **IFR can make CIRS patients with impaired Nrf2 sicker** if they can't clear the oxidative damage/toxins .This is because more drainage of toxins from the tissues into the liver may overwhelm the liver- GB axis.
- Diindolemethane (**DIM) reverses epigenetic Nrf2 blocks on mould** and other hyper-sensitive patients with Nrf2 blocks. DIM and GABA followed by B complexes , GSH , ALA can be used slowly in increasing doses . (DIM also reverses Nrf2 blocks on prostate cancer cells)
- NADPH, NMN ?? Personally found D ribose and Ubiquinol more helpful in these patients for the cost(detox requires a lot of energy hence do provide all nutrients B2,B3, B5, >.Cortisol and Ubiquinol
- Drainage is important(Coffee enema!!). Binders are important .
- **Sometimes getting out of mouldy home can help them enormously!!! At least use air filter and dehuminidifer in all significant living quarters.**

BIT MORE ON RT3 AND LIVER TOXICITY

- **High RT3 can mean liver toxicity:** “ A shift in T4 conversion to RT3 could exclusively be demonstrated for the group of hepatic cirrhosis, reflected by a significant increase in RT3. As our findings indicate normal TSH levels and a lack of clinical signs of hypothyroidism in chronic liver disease, the possibility of diverse regulating changes must be considered.”https://link.springer.com/article/10.1007/BF03349374
- “Euthyroid Sick Syndrome “ https://emedicine.medscape.com/article/118651-workup#c6
  https://emedicine.medscape.com/article/118651-overview

“In most chronic illness, defects arise in thyroid hormone metabolism, resulting in the sick euthyroid syndrome. This is characterized by a normal total T4, normal/high free T4, low total T3, low free T3, and an elevated RT3. These changes reflect a reduction in D1 activity, an increase in D3 activity”

RELATIONSHIP WITH LIVER TOXICITY AND RT3

Date	14/6/17	6/7/17	3/8/17	24/8/17	25/10/17	17/11/17	12/12/17
RT3	H682	H717	H1123	H682	H717	391	253
Comment	Daily sauna starts due to HTMA	Daily sauna	Rpt HTMA show worsening heavy metals	Daily Sauna + CE x2 starts- 14 a week	Daily Sauna +CE x14	Reduce CE to 4x a week	Phew -CE 2 a week
	Been on Zeolite ATTM for 1 yr					Note usually on very high T4 and T3 TSH -,0.005	Stop binders

PLEASE REMEMBER

THYROID!!

MOST OF THEM NEED T3

CHECK RT3!!!

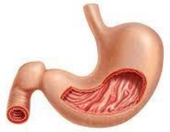
influenced by

TRH Hypothalamus

Pituitary gland

influenced by Vit A,

Vit E



+B6,B1,Zinc

stomach acid

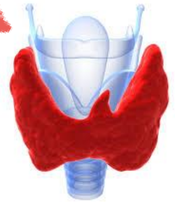
Phenylalanine

+Iron

Tyrosine

TSH- activates TPO to make T4,T3

+Iodine,selenium Vanadium,B2, C



20%

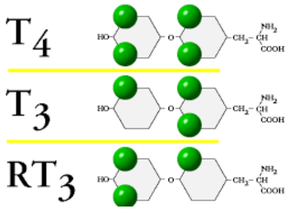
T3 10nmol/day Active and 10x stronger than T4

80% **T4** 110nmol /day -"Prohormone"

small %

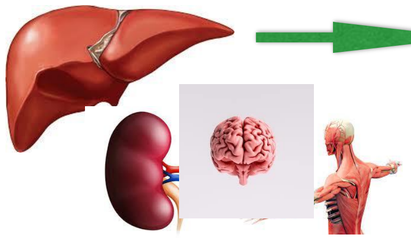
RT3

stress, infections, inflammations,liver toxicity, starvation/malnutrition increases conversion to RT3.



T3

D1,D2,D3



T3

T4 is converted to T3 in healthy liver ,kidneys, CNS, musculoskel etal system

Conversion in the liver requires

progesterone

selenium-neutralises TPO

zinc

T3Used by all cells

Salycilate metabolism

- **Metabolism of salicylates occurs through glucuronidation and by conjugation to salicyluric acid**. A small proportion (approximately 10%) of salicylates is excreted as salicylic acid in the urine, although this proportion can increase with urine that has an alkaline pH and decrease with acidic pH.

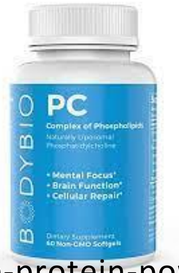
- Salicylates are metabolized principally in the liver **by the microsomal enzyme system** and are predominately conjugated with glycine to form salicyluric acid. Salicylates are also conjugated with glucuronic acid to form salicylphenolic glucuronide and salicylacyl glucuronide.

- **Salicylate, in turn, is mainly metabolized by the liver**. This metabolism occurs primarily by hepatic conjugation with glycin or glucuronic acid, each involving different metabolic pathways. The predominant pathway is the conjugation with glycin, which is saturable.

- https://pubmed.ncbi.nlm.nih.gov/2271231/

Perfect Storm-what to eat

- **Modified low oxalate /salicylate /histamine diet ??** - whatever they can tolerate-may need to change pending SIBO rx anyway
- **Digestive enzymes crucial.** Bile acids and pancreatic enzymes,Tudca, Ursofalk . Betaine HCL -if tolerate it despite CBS up regulation. Or use Gentian bitters +Bile+pancreatic enzymes before food.
- If not **Combo of ACV+lemon and ginger-**recipe see later
- **Gargling** til tear up for motility help-info up coming
- Okra pepsin with each AIP food if autoimmunity is an issue-moderate oxalates in Okra
- **Fasting** helpful-give gut a break and reduce endotoxin intrusion and Nrf2 activation.
- protein powder (some whey hemp, rice, sunflower, pumpkin seed, spirulina better)+ collagen + Cal d glucarate +-ground flaxseed ,chia (for bowel movement) may help to start with(can add others like D ribose etc)-but if SIBO the finer cannot be used.
- high dose mg cal citrate eg Mg Cal Citrate for oxalate binding and Oxycleanse etc c with emptying??suppositories
- **SIBO**?? Would need SIBO diet-biphasic or Fodmaps /Caps



https://lowhistamineeats.com/low-histamine-protein-powder/

If has CBS up regulation

- **CBS upregulation**- is more common than down regulation and can cause ammonia toxicity from sulphur
- Cannot tolerate sulphur foods including Sulforaphane! - problem as may not tolerate GSH or similar - **use tumeric, resveratrol , milk thistle but oxalate salycilates , or other physical methods-see later**
- **Stabilise blood sugar** as high glucose increase K and impair ammonia removal
- Three key amino acids needed for the urea cycle and they function to protect against ammonia toxicity. **L-Arginine, L-Citrulline and L-Ornithine.**
- **L-Ornithine** may be the most critical as it helps remove ammonia from the **brain.** Taking dosages of 500 mg of L-Ornithine in the evening and 500 mg of L-Arginine in the morning can be very helpful to aid ammonia metabolism.
- **Natural anti-microbial compounds** such as oregano oil, caprylic acid, black walnut hulls, bearberry extract, grapefruit seed extract, Pau D arco, cat's claw, slippery elm, etc. will help to reduce the quantity of the ammonia producing microorganisms.
- **Pregnenolone** reduces ammonia and ameliorate NMDA hypersensitivity.
- Celery juice(but has oxalates!), **apple cider vinegar,** kombucha(histamine!-MCAS) and coconut water kefir can help
- **Activated charcoal, Chlorophyll, Yucca root , Mg cal Citrate ,** if possible drink filter water

If has COMT issues

- Cannot break down **Noradrenaline** , hence **anxiety** is exacerbated. May be already on Lexapro continuously **depleting 5HTP and using up B1 B6 B9 B12**
- Cannot **excrete oestrogen,** more anxiety hear period, etc
- More **Copper toxicity** from CIRS and chronic illness -need zinc, molybdenum, progesterone and liver support to eliminate estrogen dominance issue , Cal D glucarate helps too,DIM ,Mg , milk thistle , turmeric, Resveratrol in small doses.
- **Medical Cannabis** esp liposomal form can help- still use cal mg citrate for oxalates (thought reported to be small amounts these patients are often scared!)
- Need **Limbic system** training if can tolerate it, otherwise simple guided meditation , weighted blanket, EFT, REMT , counsellng etc if helps.
- **Gentle sauna with binde**r with above liver support(start 1-2 a week)
- Excessive sauna can overwhelm the system, so be slow here.
- **LDN** in cream form- help endorphin level and sense of well being and may reduce MCAS by reducing the immune cascade at the TLR receptors. But also, by causing a reduction in the overall inflammation response by releasing endorphins.

Toxins (Basel). 2014 Jan; 6(1): 371–379.
Published online 2014 Jan 20. doi: 10.3390/toxins6010371

PMCID: PMC3920267
PMID: 24448208

A Review of the Evidence that Ochratoxin A Is an Nrf2 Inhibitor: Implications for Nephrotoxicity and Renal Carcinogenicity

Alice Limonciel and Paul Jennings*

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Go to:

Abstract

Several studies have demonstrated that ochratoxin A (OTA) inhibits the nuclear factor, erythroid 2-like 2 (Nrf2) oxidative stress response pathway. At the cellular level this would attenuate (i) glutathione synthesis; (ii) recycling of oxidised glutathione; (iii) activity of oxidoreductases; and (iv) phase II metabolism inducibility. The effects combined would render the cell and tissue more vulnerable to oxidative stress. Indeed, Nrf2 knock out animals exhibit increased susceptibility to various types of chemical-induced injury. Several studies have shown that OTA exposure can inhibit Nrf2 responses. Such an action would initially lead to increased susceptibility to both physiological and chemical-induced cell stress. However, chronic exposure to OTA may also act as a selective pressure for somatic mutations in Nrf2 or its inhibitor Keap-1, leading to constitutive Nrf2 activation. Nrf2 overexpression confers a survival advantage and is often associated with cancer cell survival. Here we review the evidence for OTA's role as an Nrf2 inhibitor and discuss the implications of this mechanism in nephrotoxicity and carcinogenicity.

When ‘Gentle’ does it


ADDRESS SIBO/LIBO if possible but to start with:+Butyrate

GB support: Tudca,Ursofork /Digestive enzymes eg Super enzymes /Bio-Gest my fav

Digestive support if cannot use above : gentian bitters or ACV, lemon etc

Drainage support: Xymogen Drainage,
Gentian bitters, Minerals with fulvic acid
Cell Core KL Support: “beetroot, collinsonia (stoneroot), gynostemma, marshmallow root, milk thistle seed, NAC, parsley leaf.* Together, these support fat metabolism, hepatic blood flow, and healthy urinary tract and bladder function, while helping the body carry out its natural detoxification processes.*

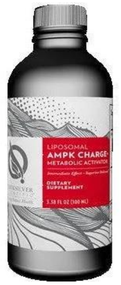
Others:Dandelion, Kidney drainage helped by herbs like Solidago, Corn Silk, and Juniper. Myrrh , Burdock, Dandelion, and Echinacea are good for blood clearing.

Other support: PC, PL, sunflower lecithin if too expensive

Basic Nutrients: A E, D K , Bs ,zinc-liposomal, topical

Some amount of physical movement
helps ‘shake the toxins from the tissue and have some sunshine!!

Gentle does it …



Binders: titrate amounts of Ultrabinder(™Fibregum Bentonite clay, Zeolite activated charcoal, aloevera silica),

Oxypowder(ozonated mg citrate- esp good for oxalate patients), Oxycleanse (Na bicarb, C, Mg bioflavonoids)

Topical /other support :

Castor Oil pack/ Rollon, Clay pack , NAC,DMSO , glutathione topical

Coffee enema suppositories- compounded /store bought

Topical hormones : Pregnenolone +-

eg Micronised /cream Progesterone +-DHEA troche in female, troche progesterone+-DHEA in males

Sodium Cromiglycate, LDN, Oxytocin troche

Calm limbic system/MCAS/CDR early

- Hope
- Liposomal L theanine- Gaba (quiksilver)-can calm brain NMDA
- Topical LDN, pregenenolone, progesterone all options
- Quercetin 1g bd
- Sodium Cromoglycate/Ketotifen 100-300 bd -can be topical, vaginal
- PEA 100mg-200mg bd
- Medical cannabis- esp liposomal form my fav Nanabis
- Meditation/counselling/EFT/Rapid eye movement therapy,QiGong,Taichi ,hummuning etc
- Gupta Program /DNRS-can still be overwhelming .
- Breathing /meditation/short cold showers ?WimHoff
- Skullcap-low dose to start with- eg Tox Ease GL or Skullcap on its own
- Oxalates deplete GSH and can be due to Oxhratoxin A
- Cal D glucarate if not given in protein powder+ _DIM (reverses Nrf2 blocking CIRS)
- Glucuronisation blocked due to mould detox consuming it -add cal d glucarate
- Add Cal Mg citrate with oxalate foods -works!!
- Salicylates sensitivities can be due to SIBO-treat this asap
- Salicylate may due to GSH depletion and poor glucuronidation , ie mould

https://www.frontiersin.org/articles/10.3389/fneur.2021.646817/full

If can tolerate sulphur and no SIBO

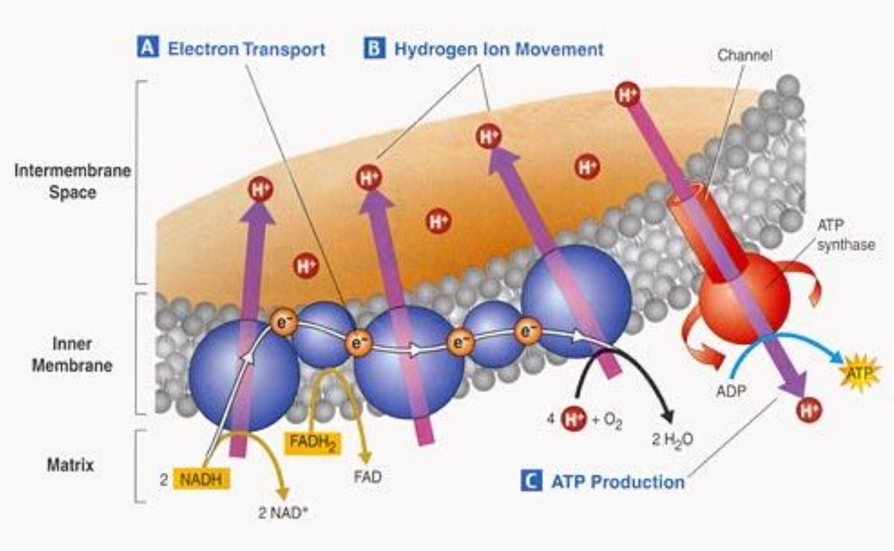
- Since mould shuts down Nrf2 and consequently GSH production, you must support phase 2 detoxification pathway in the early piece, such as adding glutathione, sulforaphane, coffee enema(providing no SIBO). Otherwise patients remain sick as they won't be able to clear the toxins that are liberated/released from tissues into the liver.
- CE helps by providing extra GSH, which is required by Nrf2 detox system,
- CE helps by clearing toxic bile from the SI hence can prevent Nrf2 shut down
- If actual CE is not possible consider CE suppositories- compounded, store bought.-see later
- add digestive enzymes crucial as said before (+Betaine HCL, pancreatic enzymes) with Bile acid that will help drain the gall bladder. Tudca can be used but Bile acid is cheaper.
- It appears detoxing mould first seem to take a huge burden off oxidative system, possibly as it is a more of a finite illness than chronic infections. Once antioxidant pathways are rejuvenated by removing toxicity burden, patients can fight infections more effectively.
- Other toxins can be detoxed following mould detox but don't seem to tax the antioxidant system as much.
- Time binders including CSM/Colesvelam/etc with liposomal GSH.
- Add high quality Sulforaphane once a day
- Berberine, high dose Quercetin, Resveratrol, curcumin, Ubiquinol ,PQQ, are all Nrf2 activators and can be used for those who cannot tolerate sulphur -can come in liquid form too.

Other supplements/spects to consider:

- PC
- Probiotics …
- Methylation support
- Pregenolone/hormones
- NADPH, NMN

Phospholipids

- **Mitochondria membranes** are critical to ATP energy production. Inadequate supply of phospholipids can r**esult in damage and result in poor ATP** production and causing more free-radical damage.
- Even other membranes within the cell including endoplasmic reticulum, responsible for making proteins and lipid (hormone) formation, are also dependent on phospholipids.
- Major component of the **surfactant in the lungs** and the **mucus in our guts**
- **Healthy membranes** of all types throughout the body are essential in facilitating movement of nutrients and clearing of toxins. Can remove bad fats and toxins, and help the cell membrane to heal.
- This is why phosphatidylcholine is very helpful but also use **digestive enzymes** that can absorb this. Sunflower lecithin can be used if cost is an issue.



https://study.com/learn/lesson/outer-mitochondrial-membrane-function-layers-composition.html

Methylation and detoxification

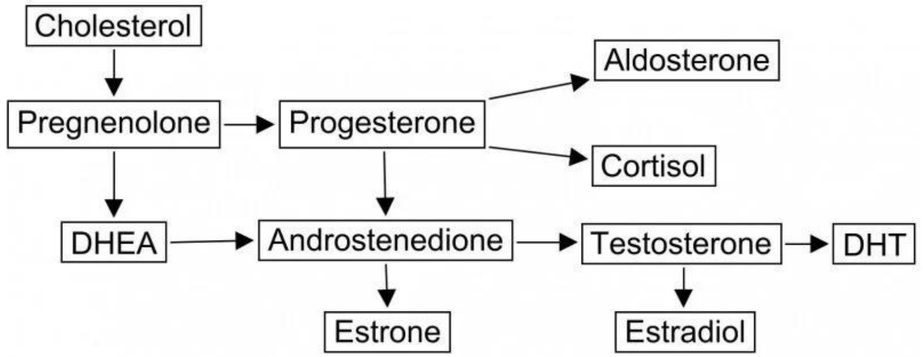
- “Methylation is an **integral part of the detoxification process** and vital to the functioning of the body. It is carried out by a group of enzymes called the methyltransferases. During methylation, active methyl (CH3) groups are transferred from one molecule to another to bring about their metabolism and elimination”. https://www.sciencedirect.com/topics/earth-and-planetary-sciences/methylation
- Histamine is detoxed 3 ways. First by **sulphation** leading to sulphate with help of molybdenum. **Methylation** (via histamine N-methyltransferase) s also involved in histamine clearance to reconstitute methionine with help of B vitamins (B2 B9 B12). Histamine is also removed by **histaminase, or diamine oxidase,** a copper enzyme.
- If methylation pathway is backed up eg due to MTHFR defect, you may be more predisposed to both sulfur and histamine intolerance due to overwhelmed detox pathways
- Molybdenum, omega three fats, B2 and B5 help with sulphation. Magnesium, B2, folate and B12 help with methylation. Copper helps with histaminase (DAO).

methylation, MTHFR, Pyrrole etc in detox

- **75.9 % population have MTHFR:**https://www.fertstert.org/article/S0015-0282(18)31021-5/fulltext#relatedArticles. In my clinic >90% have it
- Coeliac gene in my clinic is 70=80% . Not all expressed though -I always check as implication of having the gene can be serious. Silent gene expression is the problem.
- Pyrrole - in my clinic >90% have it including all my staff, family and self .
- Methylation is important- we already support by providing nutrient therapies-active Bs , glutathione, etc. Even overmethylators need detox support similarly. May go easy on active bs though.
- We can check oestrogen dominance by luteal phase se oestrodiol and progesterone without DUTCH/saliva test if finance is tight which is most of my patients
- We can check HPA axis by 24 hr cortisol/ am cortisol and ACTH. Rather than on saliva cortisol, test.
- Most have Iodine and zinc def , so do we need to check?, Se copper needs to be done with CPL otherwise not useful. How about HTMA instead as this will tell us more but doing HTMA further down the track better as true picture will not show unless patients been moving toxins around/out a bit first.
- If cost is an issue spend on gut biome, SIBO test.

Pregnenolone /Sex hormones

- **Pregnenolone** is a steroidal hormone produced mainly in the adrenal glands, but also liver, skin, brain, gonads, and even in the retina of the eye.
- HPA axis dysregulation affect cortisol production. This dysregulates blood glucose ,DHEA /Cortisol ratio
- **Increasing pregnenolone can potentially normalise** the levels of cortisol closer to normal, as well as glucose.
- **Pregnenolone** levels naturally decline with age with sex hormones, and mitochondrial function. Can be **biomarkers of aging.**



https://supplements.selfdecode.com/blog/dhea-dhea-s/

Pregnenolone

- **Brain mitochondrial functions** decline with age and that sex steroid loss is involved in the observed dysregulation of brain mitochondrial functionsIn the brain,
- **pregnenolone has a protective function of brain.** Fatigue can injure brain cells; **pregnenolone** can **protect brain cells**. **Anti-anxiolytic effects** from **pregnenolone and progesterone** can also mitigate the stress response.
- **Pregnenolone** is capable of **suppressing pro-inflammatory cytokines** induced by LPS and Pam3CSK4 in macrophages and microglial cells. The **neuroprotective role of pregnenolone** is attributed mainly to its anti-inflammatory property.
- Acts as a **GABA receptor agonist** in controls, but as an **NMDA receptor antagonist** in **hyperammonemic** rats.
- Could **restore cognitive function in hyperammonemia and encephalopathy.**
- As pregnenolone can be converted into progesterone, DHEA ,testosterone it can **support thyroid and other glands.** I**n CIRS patients** it can be a good option when HRT is required as well as adrenal support.(combo of Pregnenolone/DHEA work well in men and added progesterone can work well in women.
- **Short term** use is useful for chronic patients but stop it when they don’t need ti any more- cancer risks- breast, prostate glioma etc

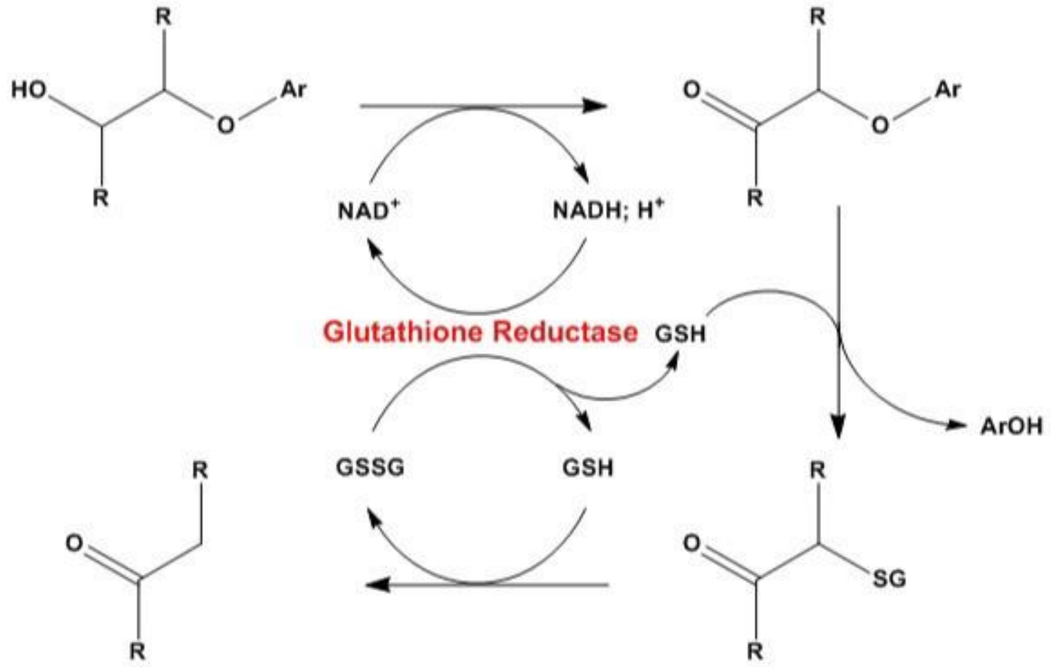
Pregnenolone/progesterone stabilises mast cells

- **Estrogen stimulates mast cells to release histamine and down-regulates the DAO enzyme**
- **histamine** stimulates the **ovaries to make more estrogen**. **Viscous cycle goes on.**
- **Progesterone stabilises mast cells, up-regulates DAO**, and can therefore reduce histamine.
- **Placenta makes DAO,** which is why mast cell activation and histamine intolerance can improve with pregnancy, beside HCG itself that can reduces general inflammation.
- Besides chronic inflammation, **dysbiosis triggers MCAS,** estrogen excess from genetic variant can disable histamine clearing enzymes HNMT(histamine N-methyltransferase) and DAO.
- SIBO impairs DAO activity(also increases salicylates)
- **B6 is crucial in regulating E/P** . (B6 200-800 mg per day can raise progesterone levels and reduce estrogen enough to improve symptoms of PMS).**B6 deficiency can exacerbate MCAS** as vitamin B6 is an essential cofactor of DAO.
- **COP causes estrogen excess** and progesterone deficiency, exacerbating MCAS

NADPH and glutathione (GSH)

(NADPH), a main cellular reductant(adds Oxygen), plays an important role in **maintaining glutathione** in its reduced glutathione modality.

This then **eliminates intracellular reactive oxygen species (ROS)**, preventing cells from oxidative damage.



https://www.jscimedcentral.com/Biotechnology/biotechnology-spid-industrial-biotechnology-made-germany-1028.php

The NOX Family of ROS-Generating NADPH Oxidases: Physiology and Pathophysiology

Karen Bedard, and Karl-Heinz Krause

01 JAN 2007https://doi.org/10.1152/physrev.00044.2005

Abstract

For a long time, superoxide generation by an NADPH oxidase was considered as an oddity only found in professional phagocytes. Over the last years, six homologs of the cytochrome subunit of the phagocyte NADPH oxidase were found: NOX1, NOX3, NOX4, NOX5, DUOX1, and DUOX2. Together with the phagocyte NADPH oxidase itself (NOX2/gp91phox), the homologs are now referred to as the NOX family of NADPH oxidases. These enzymes share the capacity to transport electrons across the plasma membrane and to generate superoxide and other downstream reactive oxygen species (ROS). Activation mechanisms and tissue distribution of the different members of the family are markedly different. The physiological functions of NOX family enzymes include host defense, posttranlational processing of proteins, cellular signaling, regulation of gene expression, and cell differentiation. NOX enzymes also contribute to a wide range of pathological processes. NOX deficiency may lead to immunosuppresion, lack of otoconogenesis, or hypothyroidism. Increased NOX actvity also contributes to a large number or pathologies, in particular cardiovascular diseases and neurodegeneration. This review summarizes the current state of knowledge of the functions of NOX enzymes in physiology and pathology.

NADPH and GSH in SARS -CoV- 2

“NAD+ supplementation can protect the lung from inflammatory injury, including cell death, caused by SARS-Cov-2 infection in both aged and young mice.”

“NADPH oxidases are responsible for catalyzing the production of ROS which is important for the functions of phagosome during immune response59. As the expressions of NADPH oxidase genes, including *Cybb*, *Ncf2*, *Ncf4*, and *Rac2*, were significantly upregulated, NADPH would be over-consumed in the lungs of SARS-CoV-2-infected mice. NADPH can provide the reducing equivalents for biosynthetic reactions and the oxidation-reduction, and allow the regeneration of glutathione (GSH)”

- Article

Treatment of SARS-CoV-2-induced pneumonia with NAD+ and NMN in two mouse models

Yisheng Jiang, Yongqiang Deng, Huanhuan Pang, Tiantian Ma, Qing Ye, Qi Chen, Haiyang Chen, Zeping Hu, Cheng-Feng Qin & Zhiheng Xu

Published: 29 April 2022

NOX-DEPENDENT SIGNALING DYSREGULATION IN SEVERE COVID-19: CLUES TO EFFECTIVE TREATMENTS

HTTPS://DOI.ORG/10.3389/FCIMB.2020.608435

SIMONA DAMIANO ET AL ,UNI NAPOLI

Reactive oxygen species (ROS) derived from NADPH oxidase enzymes (NOXs) and oxidative stress are involved in viral pathogenesis (Khomich et al., 2018). NOX enzymes, present in cell and phagosome membranes, belong to a family of six members (NOX1-5 and DUOX1 and 2) which catalyze the dismutation of superoxide anion to hydrogen peroxide and water (Bedard and Krause, 2007). NOX-driven ROS are signaling molecules regulating numerous physiological functions (Damiano et al., 2015; Damiano et al., 2019). However, a growing body of evidence points to a connection between exceeding NOX-derived ROS and multiple chronic diseases including hypertension, diabetes, and cardiovascular disease as well as obesity (Sahoo et al., 2016).

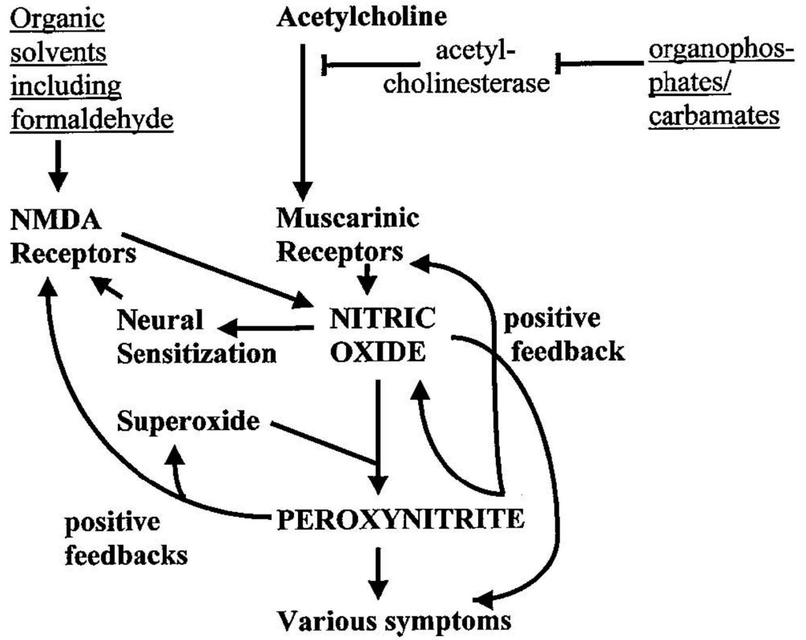
A possible common pathogenic mechanism of the main comorbidities associated with the development of the severe form of COVID-19 is the activation of the ROS generating NADPH oxidase enzymes (NOXs) and the associated oxidative stress (See *NOX Activation Is a Common Hallmark of Main Comorbidities Associated to Severe COVID-19*). Of note, endosomal NOX activation is essential for SARS-CoV cell infection and some studies have demonstrated the induction of a serum marker of NOX activation in patients affected by COVID-19 (Violi et al., 2020).

Taking into account all these evidences, we propose that a pre-existing NOX pathway dysregulation could be a determining factor in the development of the severe form of COVID-19 infection and in the onset of complications worsening the clinical outcome of disease.

https://www.frontiersin.org/articles/10.3389/fcimb.2020.608435/full

MCS

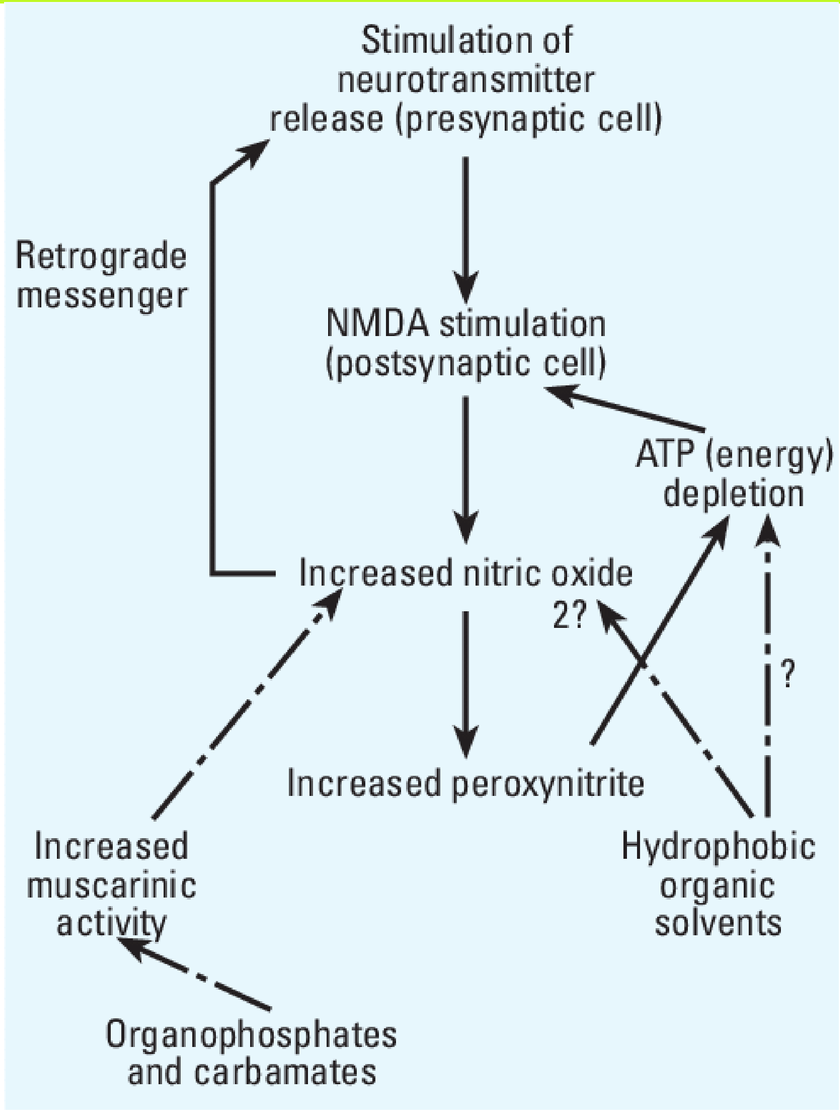
- Patients' detox pathway is **disabled by fatigued Nrf2 system and cannot trigger Nrf2 antioxidant effect.**This increases body's oxidation burden.
- **Nitric Oxide (NO)** and **Peroxynitrite (ONOO)** free-radical cascade causing inflammatory neurotoxicity , increased **Blood Brain Barrier Permeability** ,**inhibition of P450** due to **NO** said to be involved in **MCS**.
- Activation of N-methyl-D-aspartate (**NMDA**) receptors by **organic solvents** triggering **NO and ONOO** resulting in ongoing stimulation/hypersensitivity of **NMDA receptors.**
- **Pesticides such as organophosphates and carbamates** may act via **muscarinic stimulation** to produce a similar biochemical and sensitivity response.



https://faseb.onlinelibrary.wiley.com/doi/epdf/10.1096/fj.01-0861hyp

MCS : NMDA overload

- **Glutamate**, the most abundant free amino acid in the CNS, is one of the major excitatory amino acid (EAA) neurotransmitters.
- **Glutamate** produces neuronal excitation and participates in many neuronal functions, including **neuronal plasticity**. **In excess, however, it causes neurotoxicity**.
- **Glutamate overflooding** can occur in **Traumatic Brain Injury (TBI) and stroke ,** resulting in Glutamate receptor hyper-stimulation . This causes activation of **NMDA** resulting in MCS **when depleted of antioxidants.**
- **Liposomal GABA combined with L-Theanine**, and **lemon balm, chamomile, and passion flower ,niacin amide** can dampens down reactivity.
- And avoid **MSG!!!(trust me in ALL Asian foods)**
- **Again Pregnenolone** can dampen down **NMDA receptors**
- **LDN** reduces microglial activation
- Methylene Blue also helpful in calming NMDA receptor



https://www.researchgate.net/figure/Potential-vicious-cycle-mechanism-and-MCS-The-top-two-thirds-of-the-figure-represents_fig1_10588488

Summary :Standard Detoxification scenario

- Chronic inflammation blocks Nrf2 pathway
- In order to stimulate deplete antioxidant effect Phase 2 detoxification needs to be supported
- Emptying out the bile from the liver via GB is crucial
- SIBO impairs this process
- Heal SIBO, LIBO before detox is attempted
- Support GB by digestive enzymes(Betaine HCL, pancreatic enzymes, Bile/Ursofork/Tudca- Bile is cheaper eg Bio-test, Super enzymes)
- Support digestion if combined digestive not possible -gentian bitters/ACV/Lemon/Ginger/gargling
- Binders: CSM/Colesevelam for mould, Ultrabinder, Gi detox etc for others
- Coffee enema advised if SIBO is treated otherwise can make SIBO worse. Use suppositories instead
- Please support T3/Rt3
- Consider Oxalates, use diet and Mg Cal Citrate
- Emotional detox /Ongoing detox/Parasympathetic drive

Summary:Detoxification in difficult scenario

- One of the big reasons of sensitisation may be they are still stuck in unsuitable environment.
- Piecemeal approach. Starting is hard but once start the oxidative burden slowly reduces.
- Find a diet that suits them individually and supplement with liposomal, liquid, topical supplementations . Whatever they can tolerate.
- Find suitable digestive support, already discussed. Still need some form of GB and Pancreatic support
- MCAS may need to be treated at the same time or first , may be topically
- Binders would need to be gentle and slow
- SIBO/LIBO still need treatment
- Support Thyroid, Adrenals, deficiencies, hormones
- Physical detox method whatever is available to them and they can do.
- Work on limbic system/Parasympathetic drive
- Many ways to detox . Not one mode suits everyone

Physical Detox methods: useful for faster recovery

Sauna

Ionic foot bath/foot patch

Epsom salt bath

Coffee enema

Castor oil pack/rollon/Clay pack

Skin brushing

Oil pulling

Ozone therapy

Blood /plasma donation

Emotional detox should occur at the same time or before if Possible

EPSOM SALT BATH

- Epsom salts in the bath, 1cup , 12 min
- Take molybdenum 400-500mcg + B2 , 25-100mg of riboflavin , B5 250- 500mg to increase the production of sulphate from sulphur amino acids in the diet.

Benefits in detox by increasing sulphate,

Reduce inflammation and pain

Benefits skin conditions, scalp, constipation

SAUNA

- Removes many toxins through sweat; these include but are not limited to, **heavy metals, phthalates, flame retardants, Bisphenol A, pesticides and PCBs and Ochratoxin**
- Repeated sauna **optimizes stress responses** via hormesis and **heat shock proteins.**
- Sauna mimics physiological and protective responses induced during **exercise.**
- Sauna use appears to **reduce morbidity and mortality** in a dose-dependent manner in cardiovascular-related and rheumatological disease, as well as neurodegenerative diseases
- Benefits athletes seeking **improved exercise performance.**
- provides a means of preserving **muscle mass and countering sarcopenia.**
- mechanisms may include **increased bioavailability of NO** (nitric oxide) to vascular endothelium, **inhibitory effect on VEGF ,ROS production, stimulate heat shock protein-mediated metabolic activation, immune and hormonal pathway alterations(**GH,Corticosteroid, thyroid), enhanced **excretions of toxins** through increased sweating, and other hormetic stress responses.

SAUNA

- IFR acts as **antioxidant, activate cells , support metabolic process, decouples toxins water molecules, helps cellular regeneration and inhibits sympathetic nervous system.**
- IFR is **anti-inflammatory,relaxes muscles, reduces ventricular arrhythmia(possibly by decreasing VEGF)**
- Besides removing heavy metals such as Hg, Cd, As, Pd, Ni, Al, Cu, also can remove Na, K, mg and zinc
- Increases GH, corticosteroids, prolactin , improves thyroid function, **removes ammonia**

SO SAUNA AND CE…

- Try and start sauna if some enema has been done as can overwhelm the liver
- **Niacin** (50mg - 100mg of flushing type niacin), 10-30 min before sauna + binder more effective
- Adding **exercise** before sauna also helpful as can ‘shake the toxins ‘out. Approx 20-30 mins
- Follow this by CE ideal as any in the vascular system can then be removed via bowel and kidneys
- **Key is not to think of CE as a ‘colonic’.** It is not about cleaning out the bowel. And **don’t use 1 L, or will ‘explode” 200-500ml**
- It is **about introducing palmetto acid to rectal/Haemorrhoidal vein , let it travel up to portal vein stimulation GSH synthase by 700x**
- **Then Theobromine/Theophylline opening GB to drain the toxins by 700x**

SO HOW DOES COFFEE ENEMA HELP WITH NRF2

- Coffee enema(palmitic acid) **stimulate GSTs x700**
- Coffee enema can **provide GSH for Mrps to conjugate to toxins** aiding toxins and efflux from cells, **recycle GSH if Nrf2 struggles**
- Coffee enema **removes toxic bile** from SI and helps **Nrf2 to become ‘unstuck’**
- **Opposes NF-kB**

COFFEE ENEMA

General enemas were used by ancient civilisations since 5000 years ago including
Egyptians ,evidence found in one of the earliest medical textbooks such as Egyptian Ebers Papyrus, (1,500 B.C.) . Widely known and practised by Sumerians,Babylonians,Indians, Greeks, Chinese and American Indians in ancient times to the pre-revolutionary French. Louis XIV said to have had 2000 enemas in his life time,to help complexion.

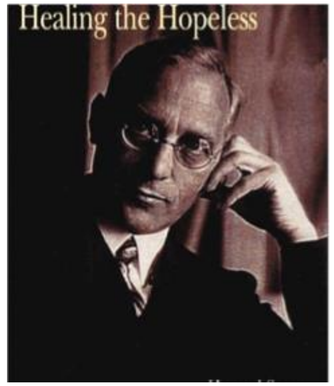
Germans started Coffee Enemas in 1917 during WW1 when the supplies dried up. Subsequently German doctors found it increased bile flow. (Prof. Meyer MD and Prof. Heubner MD at the University of Göttingen's College of Medicine).

In 1930s Dr Max Gerson incorporated Coffee enemas into his therapy for cancer.

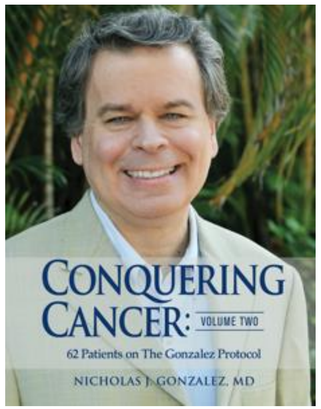
Was written in nursing textbooks and in medical

textbook MercK Manual until 1972

Coffee enema history



- In 1981 Drs Lee Wattenburg ,Sparnins ,Lam of University of Minnesota demonstrated coffee enema increased activity of certain enzyme (GST)by 700 times. (National Research Council; Diet, Nutrition, and Cancer. National Academy Press; 1982:15-7,15-8 and Cancer Res. 1982;42:1193-1198) https://www.yumpu.com/en/document/read/47176521/the-coffee-enema-its-unique-history-and-amazing-mlm- https://www.biodynamicwellness.com/wp-content/uploads/2011/04/Coffee-Enema-History-Instructions.pdf



- In 1990 an oncologist and surgeon of district hospital in Graz Austria Dr Peter Lechner reported coffee enema helps liver detoxification after clinical trial on cancer patients for 6 years and supported Gerson Therapy.

- Coffee enema was studied for feasibility for video capsule endoscopy and found mid and distal segments bowel prep tend to be better in coffee enema group (2014) https://www.ncbi.nlm.nih.gov/pubmed/25136541

- Late Dr Nicholas Gonzalez (1947-2015)also used Coffee enema as part of his cancer treatments. (inspired by orthodontist Dr William Kelly (1925-2005)

Coffee enema blends... so many options!!

coffeeenema.com.au

Coffee enema with higher palmitic acid ,
Coffee enema with turmeric
Coffee enema with collagen
Coffee enema with probiotics
Some add organosulfur, electrolytes, binders etc etc!!!

But really ANY organic coffee blend will do
Lighter it is more palmitic acid - hence choose
Medium blend first if a novice.
If patients need to add extra ingredients as not getting better despite CE,they usually are still in Mouldy homes !!

COFFEE ENEMA INSTRUCTION

- Boil filtered water -when boils add coffee granules >>>Add 1 cup of water per 1 TBS of coffee of choice planned
- Turn the heat down to simmer for 20 mins once added coffee granules
- Sieve the granules after 20 mins
- Put the solutions in mason jars - can keep safely 2-3 weeks
- Use 200-300 ml in the bag or stainless bucket , lubricate end of the tube with coconut oil
- Lie down on R side- stay for 7-12 mins- entertain yourself (you can use yoga mat to lie on or beach towel in plastic bag to lie on.
- Get up and open bowels if possible (sometimes does not happen)
- Do small volume -you don’t need to explode in the bathroom- turn you off forever!!

COFFEE ENEMA SUPPOSITORIES:

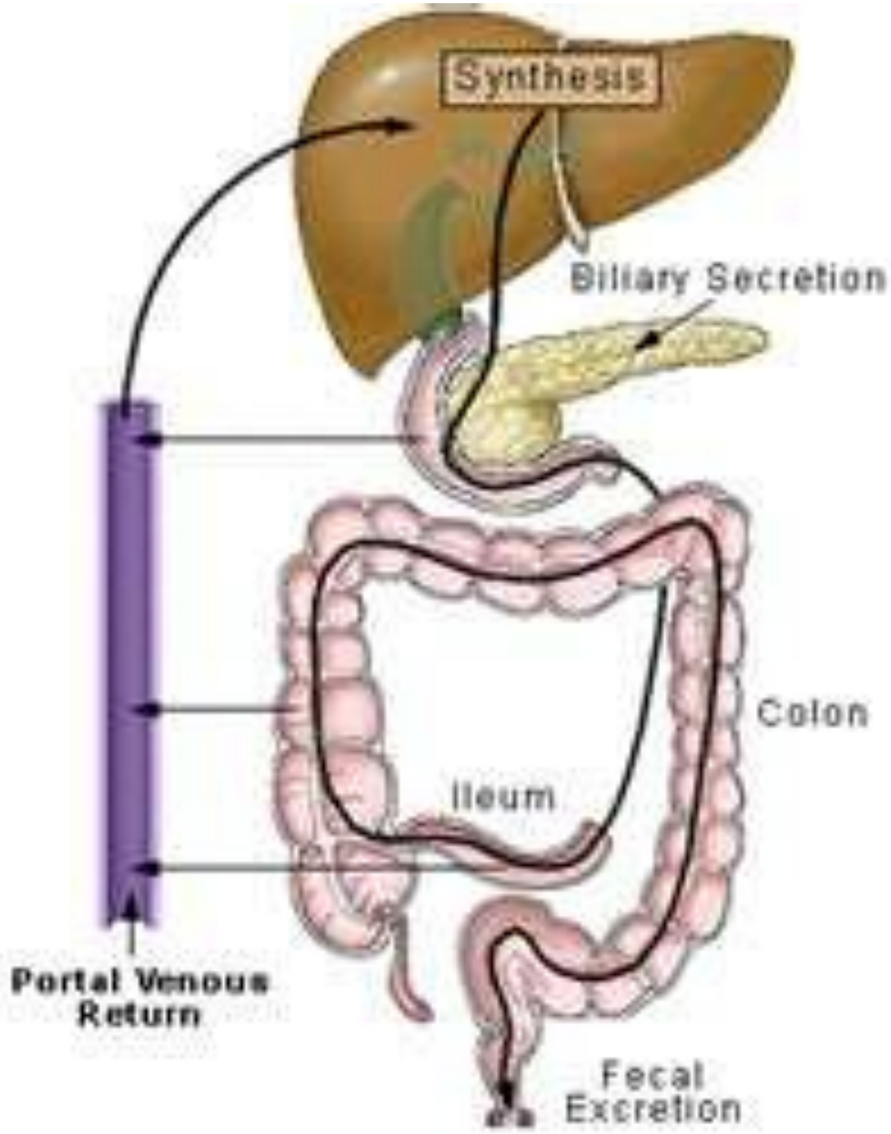
HOW DOES COFFEE ENEMA WORK?

- Coffee has 4 ingredients. Caffeine,palmitic acid, Theophylline and Theobromine

- Palmitic acid retrogradely travels up to portal vein stimulating GST-production of GSH x700

- Theophylline, Theobromine and Caffeine relax smooth muscles hence dilate blood vessels,bile duct peristalsis . Increases bile flow transiting diluted toxic bile from duodenum to the rectum.

- During the retention of the enema up to 15 minutes, and blood in the body circulates every 3 minutes - is a form of dialysis of blood across the gut wall.



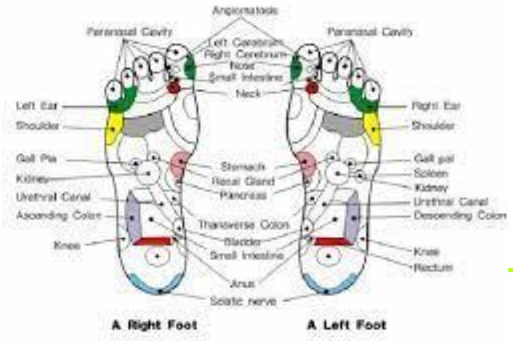
IONIC FOOT BATH/PADS ??

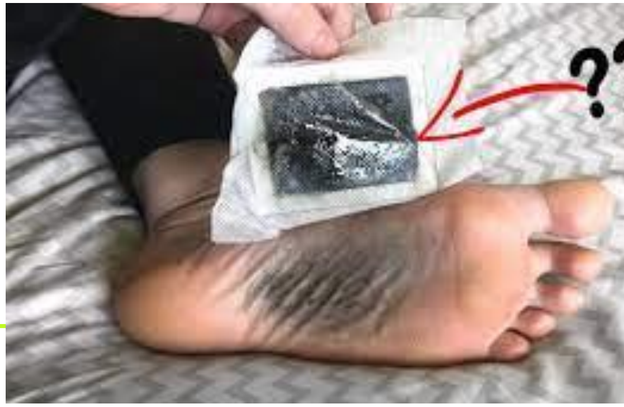
- Not many studies done on this except the one in 2012 whereAfter using Ionic food bath both iron heavy metals and HTMA did not show any differencehttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC3228292/
- This was a small study involving 3f 3m once weekly over 4 weeks.

- Feet have over 7,200 nerve endings and more than 2,000 sweat glands. The arteries and veins in our feet criss-cross in a type of heat-exchanger system. All of these components combine together to form an optimal place to begin toxin extraction from the body?

Energy is used to charge the water and split the cells into H+ and OH- ions.

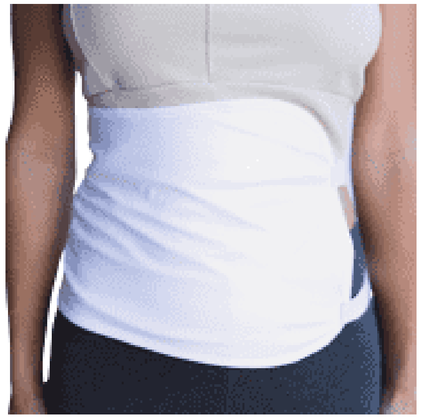
- **Colour change in foot bath water was found to be rust??**
- Improved PH Balance,
- Reduced inflammation,
- Assist the body in purging yeast,
- Liver detoxification,
- Less muscle pain.
- Support immune system
- ?Ass with acupuncture meridians





CASTOR OIL PACKS

- Castor oil is a thick, odourless oil made from the **seeds of the castor plant**, contain the **toxic enzyme ricin** deactivated during processing
- It's use dates back to ancient Egypt. Ancient Egyptians used it as lamp fuel and later for medicinal and beauty treatments — Cleopatra reportedly believed the oil would brighten the whites of her eyes.
- At present, most of the world's castor oil is produced in India. Research backs up some of its traditional uses, including laxative effects, **anti-inflammatory** properties, and the ability to help **induce labor.**
- It can be **taken orally, has laxative effect, anti-inflammatory effect, applied directly on skin for wound healing effect including acne, dandruff, ringworms, candida.**



https://integrative.ca/uploads/Resources-PDF/18-05-03-Integrative-Handout-Castor-Oil.pdf

CASTOR OIL PACKS

- Warm castor oil packs are used to a**lleviate muscle and bone pain, spasms and cramping increase Lymphatic drainage.**
- Said to i**ncrease circulation, relax muscles and disperse toxicity, decrease inflammation and strengthen immune system**
- Can also be used as a **gentle stimulant for the lungs, liver and colon.** The absorption of the oil through the skin softens and helps to **shift toxic matter and stagnant mucus from these areas.**
- Some make castor “oil packs.” —-made of cloth that is soaked in castor oil and applied to affected areas. Because of its potency, castor oil is not used in cooking or added to food
- castor oil pack is **used on the abdomen over the area of the liver to detox GB.** The idea is that the pack may help the l**iver move particles and cleanse the body**. Can be useful for those who needs GB drainage but cannot face CE.

Preparing a castor oil pack: Can also use Oil ‘Rollon’.

·Take 3 layers of cotton cloth large enough to cover area being treated. Cover each layer in oil in turn as you place them onto the skin.

· Cover with a slightly larger piece of plastic (ie a plastic bag).

· Secure with a bandage.

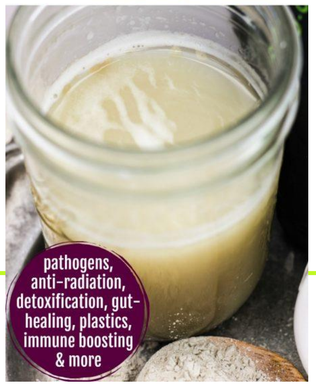
· Place a warm, not hot, water bottle over the pack.

· Leave for a minimum of two hours, replacing the water as it cools.

· Store cloth in freezer for next use.

CLAY +CASTOR OIL PACK

- **Bentonite Clay and Activated Charcoal clay can be used on its own or added to castor oil in a pack over area of the body requiring detoxification or pain. Negatively charged ingredients have been** used for thousands of years to bind to and cleanse the body of to
- Clay packs help to relieve “hot” swollen inflammations and pain especially around arthritic joints and tumours and in other areas of fluid retention.
- The **clay draws out toxins and absorbs them** and can be especially helpful when placed over the liver. It can also r**educe infection at the site of an open injury and applied around the head alleviate headaches and seizures and draw out insect bites.**
- **Calcium Bentonite clay has been taken orally to detox from pathogens, relieve constipation, treat radiation.**



OIL PULLING

- an ancient **Auveydic** practice that involves **swishing oil in your mouth 5-20 mins** to to heal gum disease and
- **remove bacteria and promote oral hygiene.** The usual oils are coconut oil, sesame oil and olive oil. Oil is spat into a bucket, toilet or paper towel after use.

  Ayurveda hypothesizes that **tongue is connected to various organs such as kidneys, heart, lungs, small intestine, spine,** etc. Oil pulling is believed to **help in the excretion of toxic heavy metals by saliva**. Oil pulling activates salivary enzymes which absorb toxins such as **chemical toxins, bacterial toxins and environmental toxins from the blood and removed from the body through the tongue.**.Thus oil pulling detoxifies and purifies the entire human body… However it is **argued that since oral mucosa is not a semipermeable membrane, toxins of the body from the blood cannot pass through it.??**
- Oil pulling **generates antioxidants** which damage the cell wall of microorganisms and kill them. These oils will attract the lipid layer of bacterial cell membranes, and cause it to stick or get attracted, and pulled to the oil and destroyed. During oil pulling, the oil gets emulsified and surface area of the oil gets increased. The process of emulsification of oil begins upon **5 min** of oil pulling..This oil will **coat the teeth and gingiva and inhibits bacterial co-aggregation and plaque formation.**Thus plaque building bacteria responsible for dental caries, gingivitis, periodontitis and bad breath are removed from the oral cavity.

OIL PULLING

- Oil pulling is observed to bring improvement in oral hygiene when practiced correctly and regularly.
- Can be safely used as an adjunct to maintain good oral hygiene and health along with the routine tooth brushing and flossing with promising positive results.
- Anand et al in their study observed **20% reduction in bacterial count upon 40 days** of oil pulling using sesame oil. Also they observed reductions in the severity of dental caries. Sesame oil was observed to possess moderate antimicrobial activity **against *S. mutans* and *L. acidophilus*.** They mentioned that toxins and bacteria from the body may be removed through the tongue and get trapped in oil and thrown out from the body.
- **60 adolescents of age 16–18 years with plaque induced gingivitis,** observed statistically significant reduction of plaque and gingival indices upon oil pulling using coconut oil.

OIL PULLING

- an *in vitro* study on oral biofilm model, **sesame oil** was observed to possess antibacterial activity against ***S. mutans***; **sunflower oil** had antibacterial activity against ***C. albicans***; and **coconut oil** was active against both ***S. mutans*** **and** ***C. albicans***

- A group of researchers compared oil pulling method using sesame oil with chlorhexidine mouthwash for **two weeks** on **20** adolescent subjects. There was statistically significant **reduction in the** ***S. mutans***

- **Proteolytic activity of three bacterial species** ***Porphyromonas gingivalis*****,** ***Tannerella forsythia*** **and/or** ***Treponema denticola*** cause 85% of halitosis associated with gingivitis, periodontitis and tongue coating. It is **also caused by Volatile sulfur** compounds like hydrogen sulphide, methyl mercaptan and dimethyl sulphide . Sood et al in their **3 week r**andomized controlled trial involving **60 subjects observed** that oil pulling with **sesame oil** was equally efficient when **compared with chlorhexidine** mouthwash in reducing oral malodor and the causative microorganisms

- **Five** researchers in a randomized controlled pilot trial involving **20** adolescent subjects concluded that oil pulling with **sesame oil is as effective as chlorhexidine** to reduce halitosis and microorganisms associated with it. This was over 2 weeks

Oral Biome: is diverse and has an important role in managing body's inflammation including :

Metabolic health, obesity ,cancer, CVD, gut health and mental health

Some of the most common bacteria in the oral microbiome include: And it is destabilisation of the balance that causes oral health issues that can impact the rest of the body:

- *Lactobacilli*
- *Bifidobacteria*
- *Porphyromonas gingivalis*
- *Staphylococci*
- *Streptococcus mutans* (and other *Streptococci* species)
- *Candida*
- *Veillonella*

https://www.rejuvdentist.com/biological-dentistry/oral-microbiome/

https://www.nature.com/articles/d41586-021-02920-w

OZONE THERAPY

Ozone therapy is a kind of detox method. It is aimed to reach the healthy circulation level of the region by increasing the oxygen supply to the diseased or damaged areas. Ozone Therapy strengthens the immune system and gives resistance to the human body.

Ozone gas is a form of oxygen. This colorless gas is made up of three oxygen atoms. In the upper atmosphere, a layer of ozone gas protects the earth from the sun's UV radiation. On ground level, however, ozone is "a

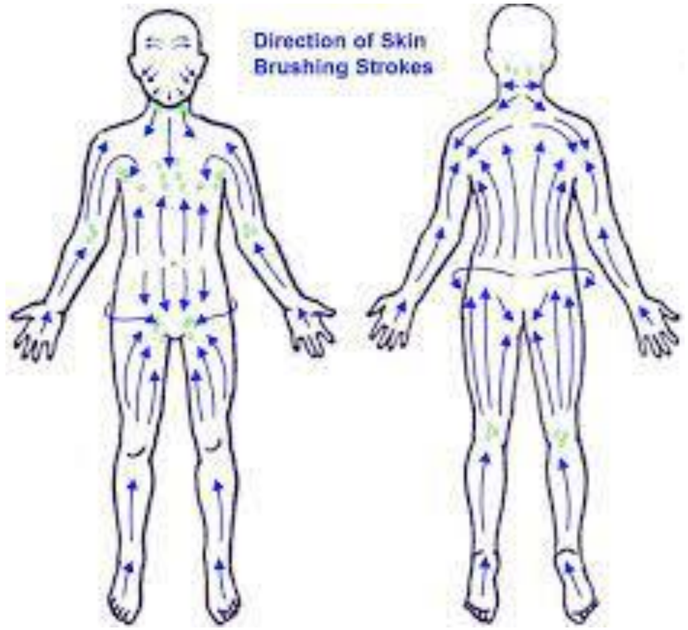
Ozone gas is harmful when a person inhales it, leading to lung and throat irritation, coughing, and worsened asthma symptoms.

High exposure can lead to lung damage and can be fatal.However, some researchers believe that ozone can have therapeutic effects in medical contexts. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3312702/ reports that ozone therapy has had the following uses:

- treating arthritis
- fighting viral diseases, such as HIV and SARS
- disinfecting wounds
- activating the immune system
- treating ischaemic heart disease
- treating macular degeneration
- treating cancer

SKIN BRUSHING

Dry brushing is a type of Ayurvedic medicine **unclogs pores in the exfoliation process**. It also helps detoxify your skin by increasing blood circulation and promoting lymph flow/drainage



Some of the benefits may include:

- stimulating the lymphatic system
- exfoliating the skin
- helping the body rid itself of toxins
- increasing circulation and energy
- exfoliation
- helping to break down cellulite

Dry brushing works by exfoliating the skin in a particular pattern towards armpits and groin.

The coarse fibers will help to remove dead skin and improve the skin’s ability to eliminate toxins through the pores.

REMOVAL OF PFAS BY BLOOD DONATION

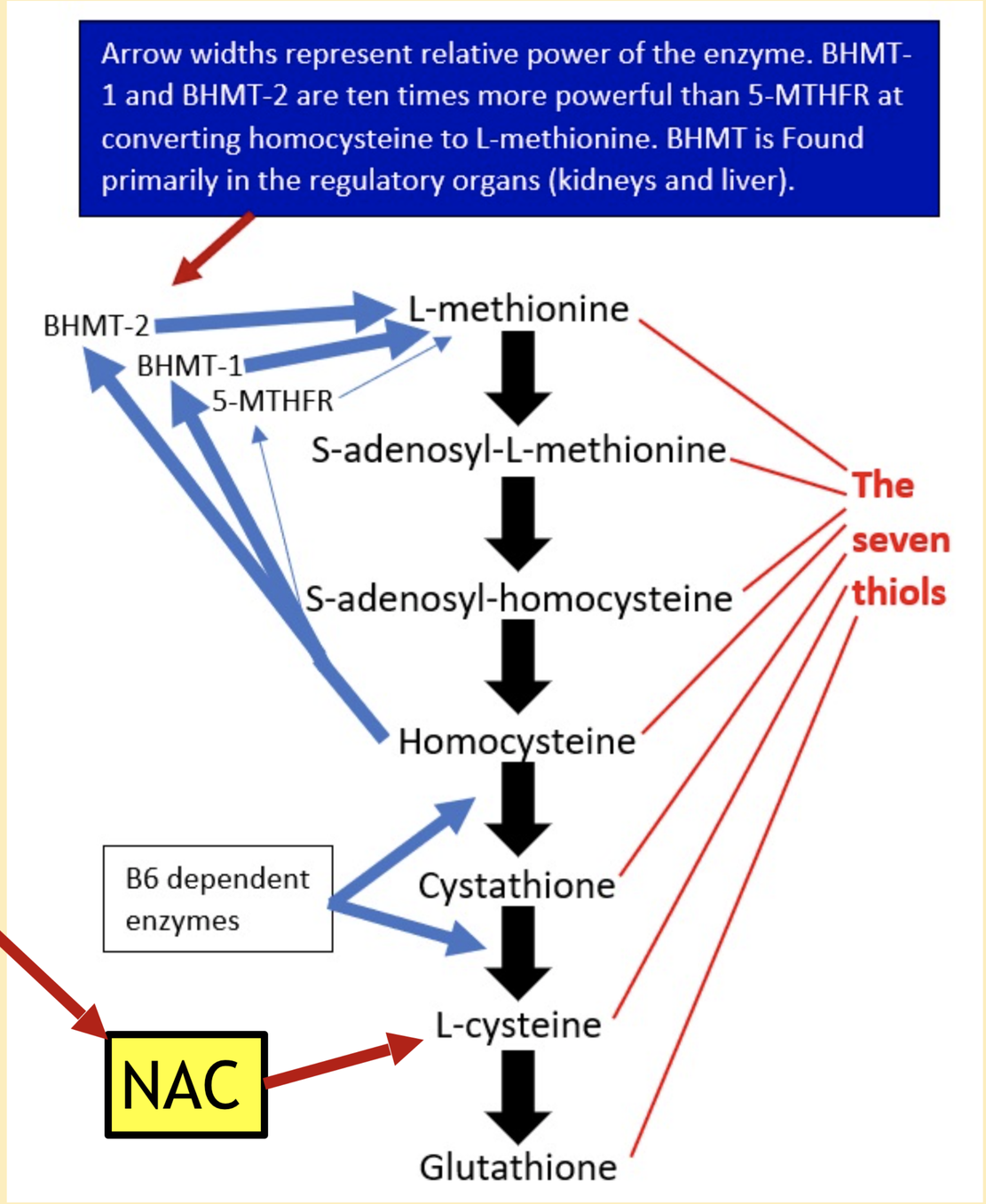
- Fire fighter Tilbury realised blood donator mates had lower levels of PFA foam , so did women.
- Donation of plasma is effective as the toxins are attached to protein. Hence removing plasma via blood donation can reduce PFAS levels,
- Conducted in partnership with CSIRO and the University of Western Australia, the research found that PFAS chemicals (per- and poly-fluoroalkyl substances) can be removed from contaminated water via Australian native rushes - *Phragmites australis, Baumea articulata,* and *Juncus kraussii, Phragmites australis*, otherwise known as the common reed, removed legacy PFAS contaminants by 42-53 per cent from contaminated surface water (level: 10 µg/L).https://www.csiro.au/en/news/news-releases/2022/hydroponic-native-plants-to-detox-pfas-contaminated-water
- What other toxins can we reduce by this method? **Gadolinium** from MRI? As it is bound to albumin:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2822463/
- At present copper and zinc Trisodium (DTPA) is said to help bind via IV (method by Dr.Richard Semelka MD)but not available in Australia. EDTA is another method considered.

PFAS REMOVAL BY AUSTRALIAN NATIVE PLANT

- They’re the non-stick on Teflon cookware, the stain resistance in Scotchgard, and the suppression factor in firefighting foam, but while the staying power of PFAS chemicals was once revered, it’s now infamous as PFAS substances continue to infiltrate the environment and affect human health.
- Now, new research from the University of South Australia is helping to remediate the ‘indestructible’ PFASs as scientists show that Australian native plants can significantly remediate PFAS pollutants through floating wetlands to create healthier environments for all.
- Conducted in partnership with CSIRO and the University of Western Australia, the research found that PFAS chemicals can be removed from contaminated water via Australian native rushes - **Phragmites australis, Baumea articulata, and Juncus kraussii.**
- Phragmites australis, otherwise known as the common reed, removed legacy PFAS contaminants by **42-53** per cent from contaminated surface water (level: 10 µg/L).

https://www.csiro.au/en/news/news-releases/2022/hydroponic-native-plants-to-detox-pfas-contaminated-water

NAC is not naturally found in the system, it needs to be metabolized to L-cysteine to become biologically active.



Presenting peer-reviewed original research papers that were co-authored with faculty at the University of Minnesota Medical School in Duluth, MN

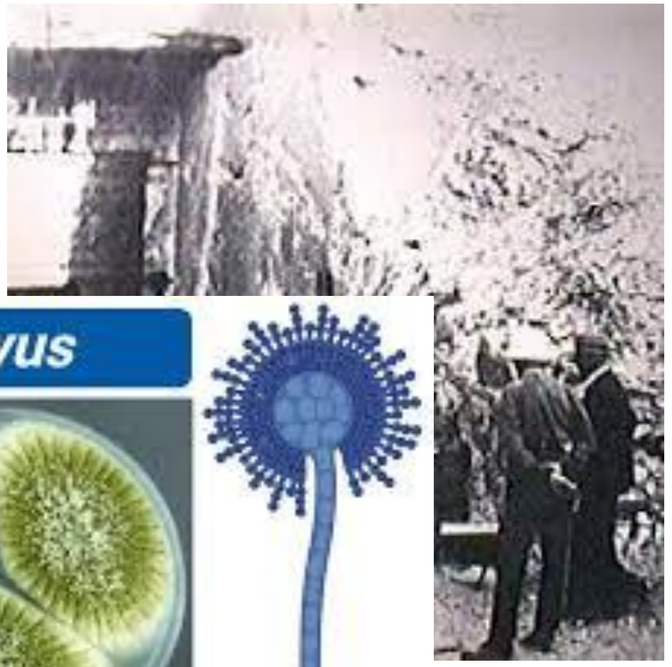
Neuro Research

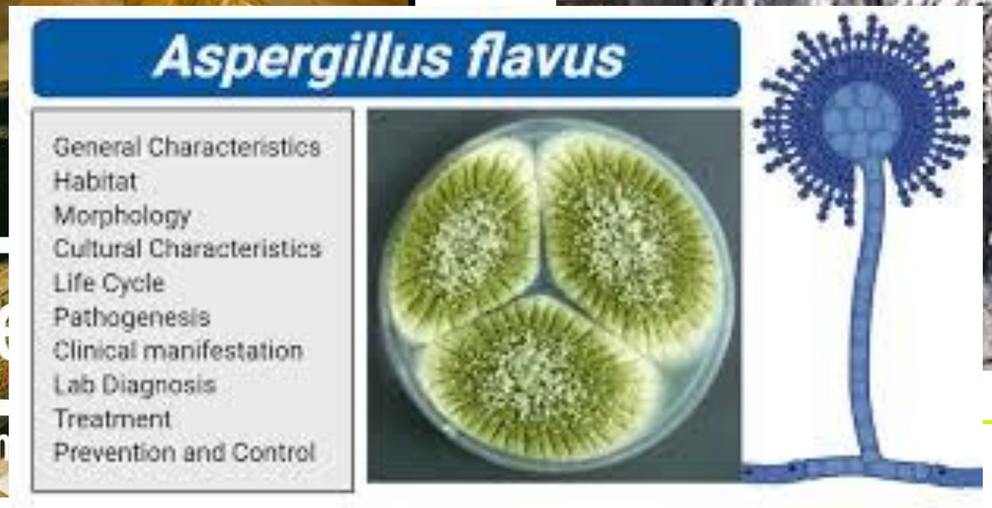
A Medical Education Company

These statements have not been evaluated by the Food and Drug Administration (FDA). These nutrients are not intended to diagnose, treat, cure, or prevent any disease.

Aspergillus Flavus

- Nov 4th 1922 Howard Carter opened Tutankhamen's tomb . 6 people including Carter's financier Lord Carnarvon died subsequently associated with' blood poisoning' and others of murder or lung condition. 12 Others involved in similar excavations died
- 1999 A Flavus discovered in tombs





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NF-κB in Oxidative Stress
Krithika Lingappan1

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Xiaoyun Guo, Yi Chen, Rachel Steinmetz, Siqi Hong, Hui He, Yachang Zeng and Qinghang Liu
Originally published16 Oct 2019https://doi.org/10.1161/res.125.suppl_1.163Circulation Research. 2019;125:A163

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Nrf2 signaling pathway: Pivotal roles in inflammation

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A closer look into NADPH oxidase inhibitors: Validation and insight into their mechanism of action
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The Metabolism of Glucosinolates by Gut Microbiota
Kalina Sikorska-Zimny1,2,* and Luciano Beneduce3
Jean-Louis Guéant, Academic Editor

Nrf2 signaling pathway: Pivotal roles in inflammation

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Suryakant K Niture 1, Raju Khatri 1, Anil K Jaiswal 2
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Sulforaphane treatment of autism spectrum disorder (ASD)
Kanwaljit Singh, Susan L. Connors, Eric A. Macklin, **+3**
, Kirby D. Smith
, Jed W. Fahey
, Paul Talalay ptalalay@jhmi.edu
, and Andrew W. Zimmerman ptalalay@jhmi.edu
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October 13, 2014
111 (43) 15550-15555
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The Chinese herbal formula Free and Easy Wanderer ameliorates oxidative stress through KEAP1-NRF2/HO-1 pathway
Chunlan Hong 1, Jingming Cao 1, Ching-Fen Wu 1, Onat Kadioglu 1, Anja Schüffler 2, Ulrich Kauhl 3, Sabine M Klauck 4, Till Opatz 3, Eckhard Thines 5, Norbert W Paul 6, Thomas Efferth 7
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Bardoxolone methyl and kidney function in CKD with type 2 diabetes
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Nrf2: A Potential Target for New Therapeutics in Liver Disease
AM Bataille1 and JE Manautou1

Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases
Hemant Kumar 1, In-Su Kim, Sandeep Vasant More, Byung-Wook Kim, Dong-Kug Choi
PMID: 24292194 DOI: 10.1039/c3np70065h

Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases
Hemant Kumar 1, In-Su Kim, Sandeep Vasant More, Byung-Wook Kim, Dong-Kug Choi
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Role of NRF2 in protection of the gastrointestinal tract against oxidative stress
Akinori Yanaka1,*

Relations between serum levels of TSH, TBG, T4, T3, rT3 and various histologically classified chronic liver diseaseOctober 2014Journal of Endocrinological Investigation 3(4):379-83
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Activation of NRF2 by topical apocarotenoid treatment mitigates radiation-induced dermatitis
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Berberine activates Nrf2 nuclear translocation and inhibits apoptosis induced by high glucose in renal tubular epithelial cells through a phosphatidylinositol 3-kinase/Akt-dependent mechanism
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Vitamin E prevents NRF2-suppression by allergen in asthmatic alveolar macrophages *in vivo*
Ryszard Dworski, MD, PhD,a,* Wei Han, MD,a Timothy S. Blackwell, MD,a,b,c,d Aimee Hoskins, RN, BSN,a and Michael L. Freeman, PhDe
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Nrf2 Suppresses Allergic Lung Inflammation by Attenuating the Type 2 Innate Lymphoid Cell Response
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NRF2 Activation with Protandim Attenuates Salt-Induced Vascular Dysfunction and Microvascular Rarefaction
Jessica R. C. Priestley,*,1 Katie E. Fink,*,1 Joe M. McCord,2 and Julian H. Lombard1
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Can Activation of NRF2 Be a Strategy against COVID-19?
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Grow you own Broccoli sprouts

Step 1: Put two tablespoons of the broccoli seeds into the mason jar. Cover with a few inches of fresh filtered water and let the seed sprouts soak.
Place the sprouting lid (or fine mesh strainer lid) on the jar and put the jar in a warm and dark place for 8-12 hours so the seedlings can sprout. Next, try placing the jar on the counter on top of your dishwasher and cover with a towel. The broccoli seeds love the moist heat from the dishwasher and will have no problem with germination in such an environment.

Step 2: Drain the water off the seeds on day two. Lay the jar upside down on an angle inside a bowl to help remove excess water. Keep the jar in a slightly warm and dark place.

Step 3: Rinse the sprouts 2-3 times a day and drain them after each rinse. During the day, leave the sprouts by the windowsill, so they get direct sunlight. By day three, seeds should be sprouting. Keep the jar in warm place until the sprouts are about one inch long.
Once you see dark green leaves – generally 3-4 days after sprouting- it is time to harvest them.

https://thecoconutmama.com/broccoli-sprouts/

THANK YOU!!!