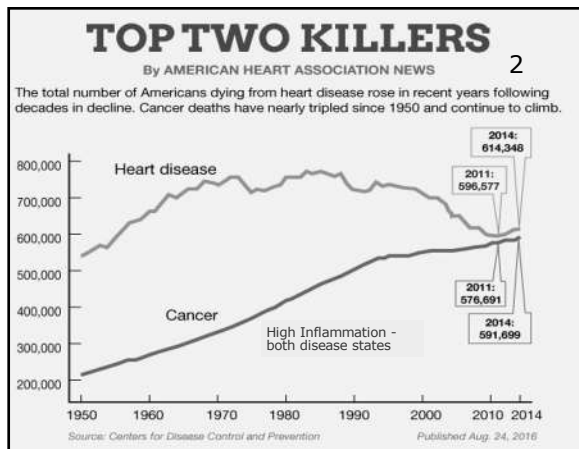
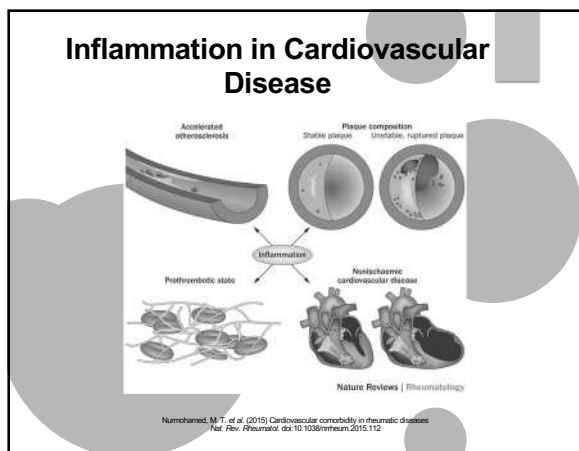


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2



3

Inflammation in Cancer and Cancer Treatment

► Inflammation and cancer: Till death tears them apart. Raposo TP. Et al. Veterinary Journal. 2015.

The diagram illustrates the progression of cancer from infection to treatment. It starts with 'Infection' (Allyl, Infectious Disease, Endotoxins, Obesity) leading to 'Tumor Initiation'. This is followed by 'Inflammation arising from infection, autoimmunity or the microenvironment' leading to a 'Tumor ball'. Further 'Inflammation arising from the Tumor ball' leads to 'Cancer Therapy'. A box lists factors: Microplasma, Lymphocytes, Chemokines, Cytokines, MMPs, Interleukins, ROS, and TM. 'Chemokines Substrates' are also shown.

4

Neuroinflammation: The Brain on Fire

The image shows a human brain with a thick layer of white smoke or fire rising from its surface, symbolizing the concept of neuroinflammation.

5

Neurodegenerative Diseases: Autism to Alzheimer's

The diagram shows the progression from infectious agents to neuronal death. Infectious agents lead to 'Rusting Microglia' and 'Astrocyte Microglia'. These lead to 'Neurotoxins' and 'Neuron'. 'Neurotoxins' also lead to 'Neuron'. 'Neuron' leads to 'Neuronal Death'. 'AB peptides, α-Syn' are shown above 'Neurotoxins'. 'MPO, ROS, IL-1, IL-6, TNF' are shown below 'Astrocyte Microglia'.

6

Alzheimer's Neuroinflammation

7

- ▶ Accumulation of protein aggregates
 - ▶ Extracellular: B-amyloid plaques
 - ▶ Intracellular: Neurofibrillary tangles (NFT)
 - ▶ Cause loss of synaptic function leading to neuronal death
- ▶ Microglial activation
- ▶ Astrocyte activation
- ▶ Pro-inflammatory cytokines near B-amyloid protein deposits and NFT

7

Autism: An emerging neuroimmune disorder in search of therapy. Theoharides TC, Et al. Expert Opinion in Pharmacother. 2009. 10(13)P:2127-2143

8

8

Neuroinflammation Markers in ASD

9

- ▶ Microglial activation
- ▶ Astrocytic activation with elevated levels of GFAP (glial fibrillary acidic protein)
- ▶ Proinflammatory profile of cytokines in the brain, CSF and blood
- ▶ Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation

9

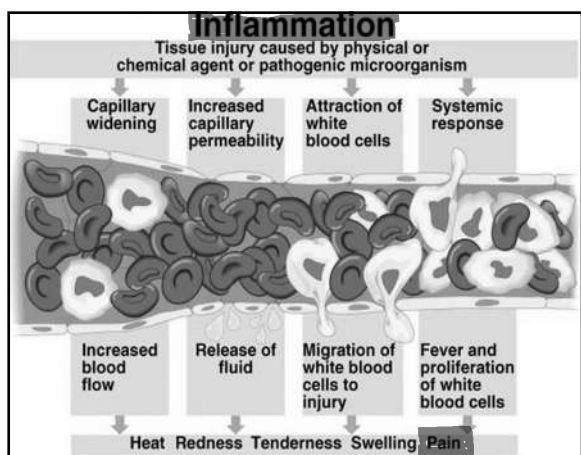


10

Acute vs Chronic Inflammation 11

- ▶ **Acute Inflammation**
 - ▶ Normal immune response to injury or infection
- ▶ **Chronic Inflammation**
 - ▶ Prolonged abnormal immune response

11



12

Normal Resolution of Immune Response 13

The diagram illustrates the process of resolving an immune response. It shows neutrophils at a site of inflammation. Key processes labeled include: 'Neutrophil activation stop', 'Neutrophil Apoptosis', 'Anti-inflammatory cytokines', 'Polarization of the macrophages', and 'Apoptotic neutrophil clearance by macrophages'. The diagram shows neutrophils becoming apoptotic and being cleared by macrophages, while macrophages polarize and release anti-inflammatory cytokines to stop further neutrophil activation.

13

If neutrophils are not phagocytized, then they break open and release enzymes and cytokines that damage tissue leading to chronic inflammation

TheScientificWorld

Role of Neutrophil Apoptosis in the Resolution of Inflammation

Oliver H. Baker and James G. Flynn
Department of Microbiology, Immunology and Pathology, and Cell Biology, University of Arkansas at Little Rock, Little Rock, Arkansas, USA

Received: 04/28/2019; Revised: 05/20/2019; Accepted: 06/10/2019; Published: 06/10/2019

Neutrophil phagocytosis plays a critical role in host response to infection and tissue repair. Host injury, triggered by a stimulus for resolution of inflammation, including microbial clearance, disrupts signaling in the neutrophil control panel, in the membrane and nucleus of neutrophils. Disrupted signaling and/or impaired function of membrane receptors and protein kinases leads to neutrophil apoptosis. The process of neutrophil apoptosis and subsequent uptake by the macrophages, especially when not the subject of phagocytosis, is a critical step in the resolution of inflammation. Neutrophil apoptosis is a regulated process, involving signaling pathways that include the mitochondrial pathway, leading to the activation of caspases and the release of cytochrome c, which in turn leads to the formation of apoptosomes and the activation of caspases. This process is regulated by a variety of factors, including cytokines, chemokines, and growth factors. Neutrophil apoptosis is a critical step in the resolution of inflammation, and its dysregulation can lead to chronic inflammation and tissue damage.

INTRODUCTION

Inflammation is a protective response that is essential for a variety of reasons, including its protective and reparative functions. Inflammation is a complex process that involves the recruitment of immune cells to the site of injury or infection, the release of signaling molecules, and the activation of various cellular processes. Neutrophils are the first cells to arrive at the site of inflammation, and they play a critical role in the resolution of inflammation. Neutrophils are highly motile and are able to migrate through the endothelium and into the tissue. Once in the tissue, they can phagocytose and kill pathogens, and they can release signaling molecules that recruit other immune cells. Neutrophils also play a role in tissue repair and remodeling. However, if neutrophils are not properly regulated, they can cause tissue damage and contribute to chronic inflammation. Neutrophil apoptosis is a critical step in the resolution of inflammation, and its dysregulation can lead to chronic inflammation and tissue damage.

14

Nrf2: Nuclear Factor 2 15

- ▶ Master regulator of the antioxidant system
- ▶ Mechanism: A Nrf2 activator releases protein into the cell nucleus where it binds to DNA and activates antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase and these enzymes can neutralize up to 1 million free radicals

The diagram shows a cell with an 'Activator' entering the cell. The activator releases 'Nrf2' protein into the cytoplasm. Nrf2 then enters the nucleus and binds to DNA, activating 'Antioxidant Enzymes'.

15

Nrf2: Nuclear Factor 2 Activators

1
6

- ▶ Resveratrol
- ▶ Curcumin
- ▶ Quercetin
- ▶ Sulforaphane
- ▶ EGCG (tea)
- ▶ Allium (Garlic)
- ▶ Polyphenols
- ▶ Ginger
- ▶ Cocoa
- ▶ Carnosol (Rosemary)
- ▶ Coffee
- ▶ Eugenol (Clove)
- ▶ Ellagic Acid
- ▶ Brassica (Cabbage family)
- ▶ Molecular H2
- ▶ Bacopa
- ▶ Ashwagandha

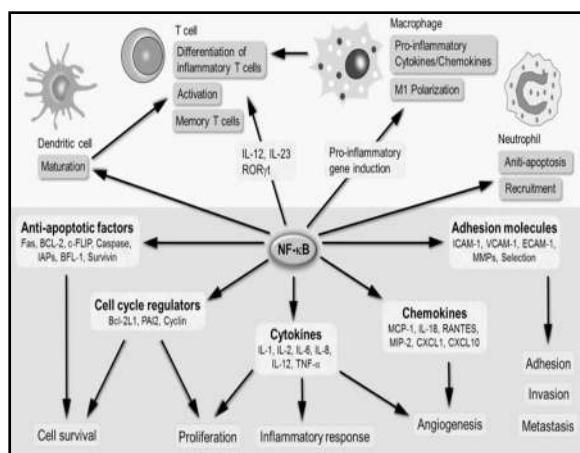
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NF-κB: Nuclear Factor Kappa B

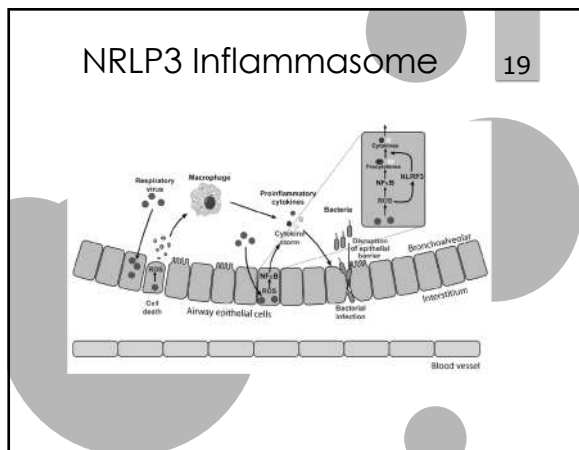
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- ▶ Transcription Factor
- ▶ Activated by oxidative stress
- ▶ Increase in pro-inflammatory cytokines

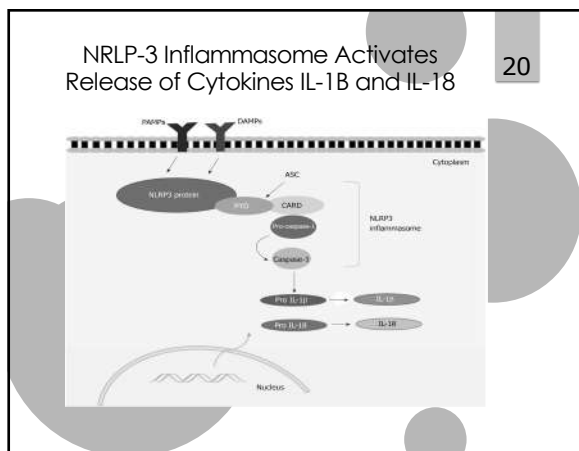
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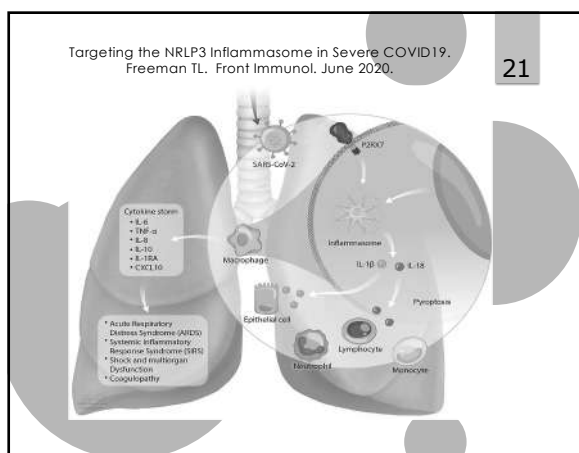
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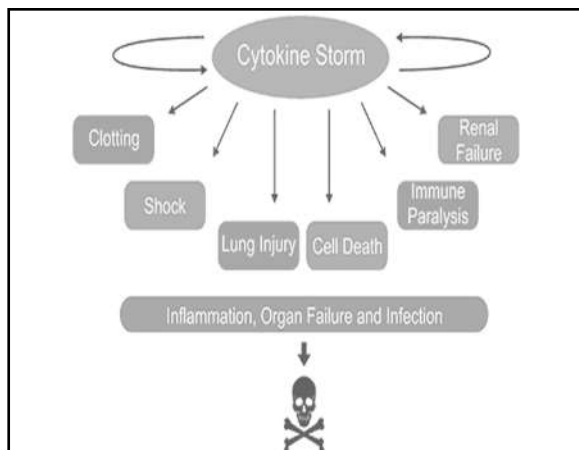
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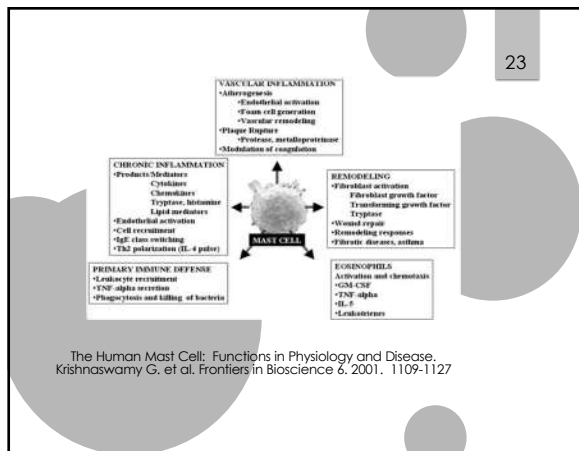
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Causes of Inflammation

- ▶ Infections
- ▶ Toxins/Environmental Chemicals
- ▶ Medications
- ▶ Obesity
- ▶ Hormonal Imbalance
- ▶ Poor Diet
- ▶ Food Sensitivities/Allergies
- ▶ Injury
- ▶ Mental and Emotional Stress

25

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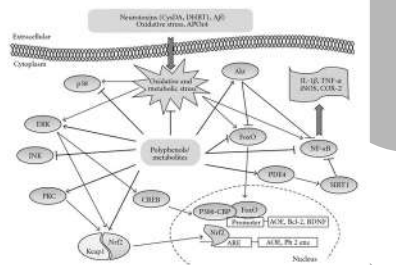
Anti-inflammatory Whole Food Organic Diet



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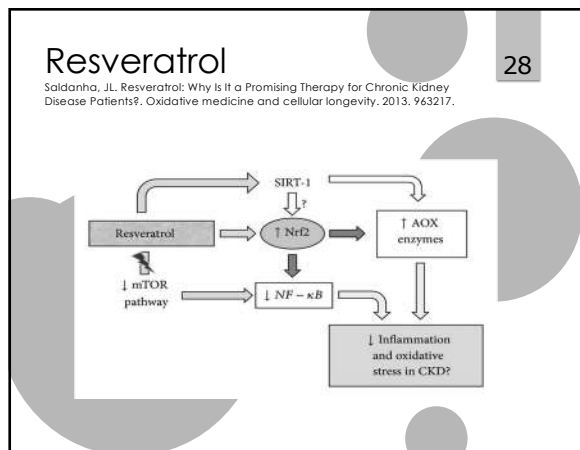
26

Dietary Polyphenols as Modulators of Brain Functions: Biological Actions and Molecular Mechanisms Underpinning Their Beneficial Effects.
Oxidative medicine and cellular longevity. Vauzour, David. (2012)

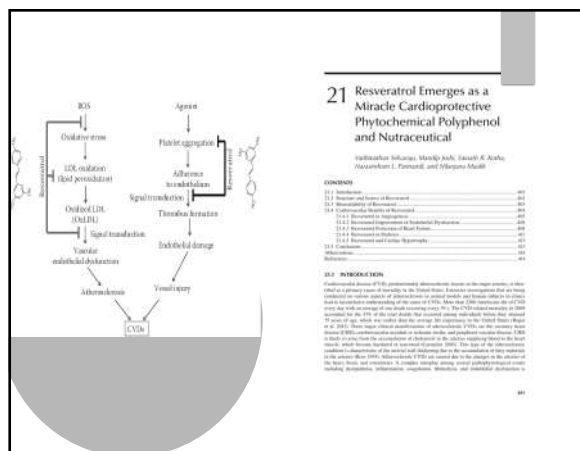


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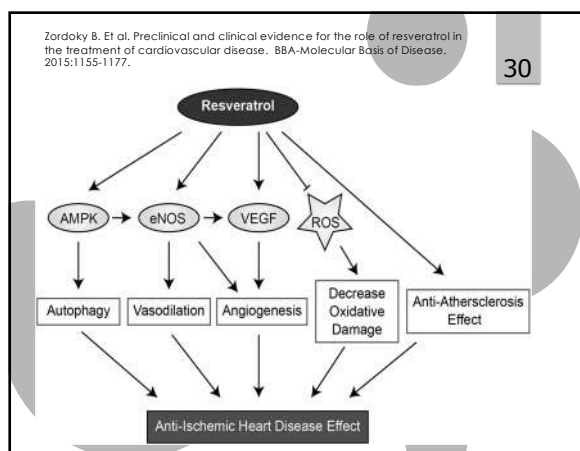
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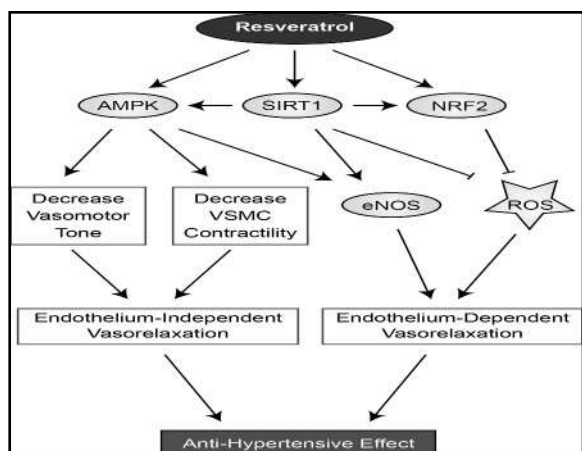
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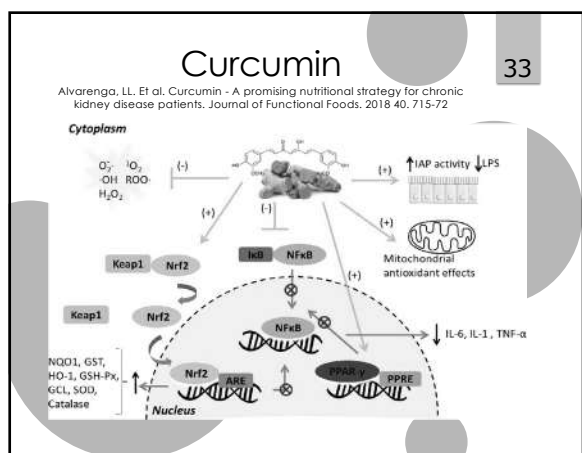


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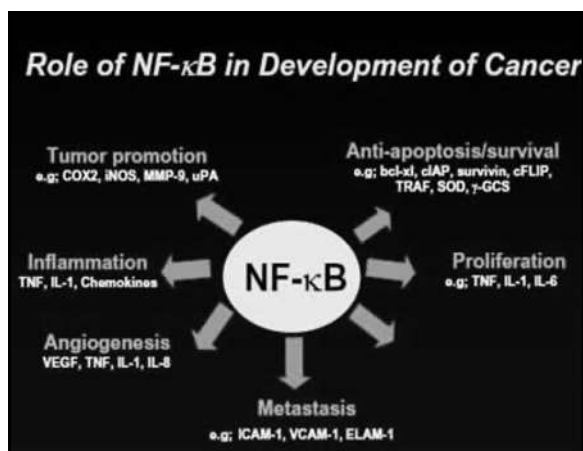
Role of dietary phenols in mitigating microglia mediated neuroinflammation
 Rangarajan P et al. Neuromolecular Med 2016 Sep.

- ▶ Review of polyphenols: Curcumin, Resveratrol, Quercetin, Luteolin
- ▶ Decrease sustained activation of the microglia (innate immune cells of the CNS)

32



33



34

► Curcumin helpful for multiple pathways of decreasing inflammation and helping in cancer prevention and formation

Potential applications of curcumin and its novel synthetic analogs and nanotechnology-based formulations in cancer prevention and therapy

Abstract
Curcumin is a natural polyphenolic compound in the rhizome of the turmeric plant (*Curcuma longa*) that has been extensively studied for its potential applications in cancer prevention and therapy. It has been shown to inhibit multiple pathways involved in cancer development, including inflammation, cell proliferation, and angiogenesis. This review discusses the potential applications of curcumin and its novel synthetic analogs and nanotechnology-based formulations in cancer prevention and therapy.

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35

► Curcumin decreases response to environmental toxins through AhR

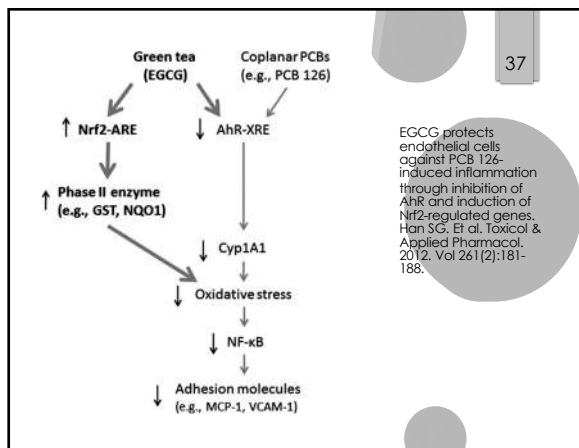
► Preventative from environmental toxin induced inflammation

Curcumin attenuates cytochrome P450 induction in response to 2,3,7,8-tetrachlorodibenzo-p-dioxin by ROS-dependently degrading AhR and ARNT

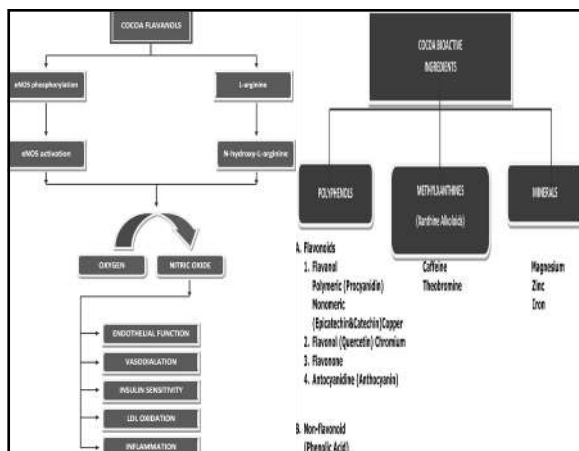
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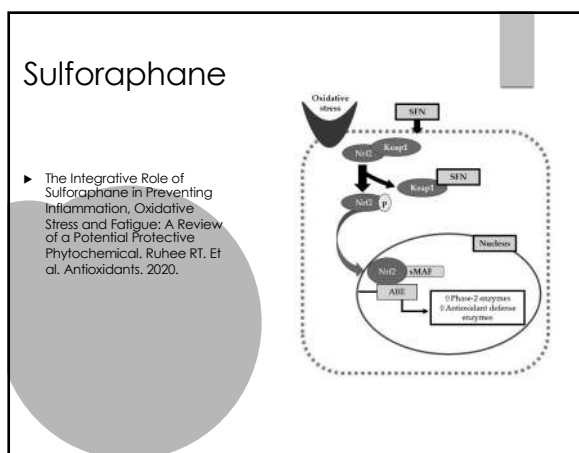
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39

Induction of phase 2 antioxidant enzymes by broccoli sulforaphane: perspectives in maintaining the antioxidant activity of vitamins A, C, and E. Boddupalli S. et al. Front. Genet., 24 January 2012

40

40

Boswellia Inhibits 5-Lipoxygenase

41

Arachidonic acid is a precursor in the production of eicosanoids:

- The enzymes **cyclooxygenase** and **peroxidase** lead to prostaglandin H2, which in turn is used to produce the prostaglandins, prostacyclin, and thromboxanes.
- The enzyme **5-lipoxygenase** leads to 5-HPETE, which in turn is used to produce the leukotrienes.
- Arachidonic acid is also used in the biosynthesis of anandamide, and some is converted into HETEs and ETs by epoygenase.
- The production of these derivatives and their action in the body are collectively known as the "arachidonic acid cascade"

41

Neurologic Benefits of Ashwagandha


42

- ▶ Increase BDNF
- ▶ Increase neurogenesis
- ▶ Decrease cortisol and stress- adaptogen
- ▶ Increase memory, learning, cognition
- ▶ Improved sleep
- ▶ Increase telomerase activity
- ▶ Decrease anxiety, depression
- ▶ Improve mood
- ▶ Decrease b-amyloid protein(Alzheimer's)
- ▶ Decrease synuclein protein(Parkinson's)
- ▶ Decrease oxidative stress
- ▶ Anti-inflammatory

42

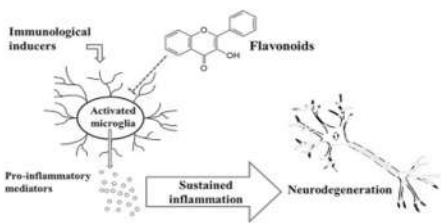
Flavonoids

- ▶ Group of polyphenolic compounds found in fruits, flowers, seeds, and vegetables
- ▶ Flavonoids are naturally occurring molecules with
 - ▶ antioxidant
 - ▶ cytoprotective
 - ▶ anti-inflammatory actions
- ▶ Inhibit IgE mediated histamine release
- ▶ Decrease production of proinflammatory cytokines
- ▶ Down-regulate mast cell activation



Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells. Park HH, et al. Arch Pharm Res. 2008 Oct;31(10):1303-11

43



44

Anti-inflammatory effects of flavonoids in neurodegenerative disorders. Spagnuolo C, et al. Eur. J. Of Med Chem. 2018.

44

Luteolin: Flavonoid

- ▶ Anti-oxidant
- ▶ Anti-inflammatory
- ▶ Inhibits MC degranulation
- ▶ Inhibits MC cytokine release (Cromolyn and Ketotifen do not)
- ▶ Decreases microglial activation and proliferation
- ▶ Decreases autoimmune T cell activation
- ▶ Neuroprotective

▶ Spectrum of mast cell activation disorders. Petra A, et al. Expert Rev. Clin. Immunol. 10(6), 729-739 (2014)

45

45

Quercetin:

- ▶ Type of Flavonoid
- ▶ Anti-inflammatory
- ▶ Inhibit Mast Cell activation

46

Interrelationship between Inflammation and Oxidative Stress.

Picco A, Lezza AMS, Leeuwenburgh C, Pasco V, Calvani R, Landi F, Bernabei R, Marzetti E. Fueling Inflamm-Aging through Mitochondrial Dysfunction: Mechanisms and Molecular Targets. International Journal of Molecular Sciences. 2017; 18(5):933.

47

Oxidative Stress

Definition

- ▶ Imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects through neutralization by antioxidants

48

Anti-oxidants

- ▶ Tocotrienols/Tocopherols: vitamin E
- ▶ Glutathione
- ▶ Vitamin C
- ▶ Alpha-lipoic acid
- ▶ Molecular Hydrogen

49

49

Vitamin E: Tocopherols and Tocotrienols

50

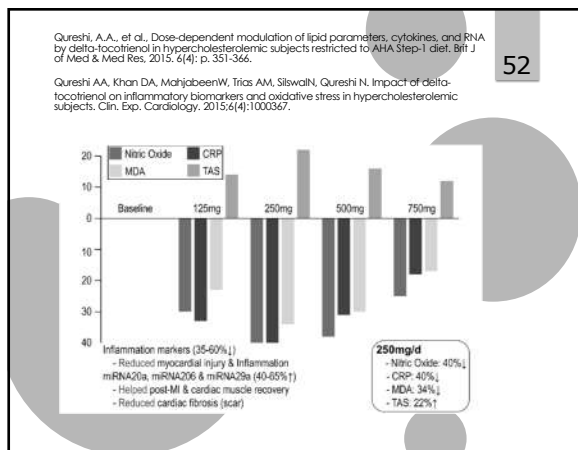
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Tocotrienols

- ▶ Protection against:
 - ▶ Oxidative Stress
 - ▶ Inflammation
 - ▶ Neurodegeneration
 - ▶ Cancer
 - ▶ Cardiovascular disease

51

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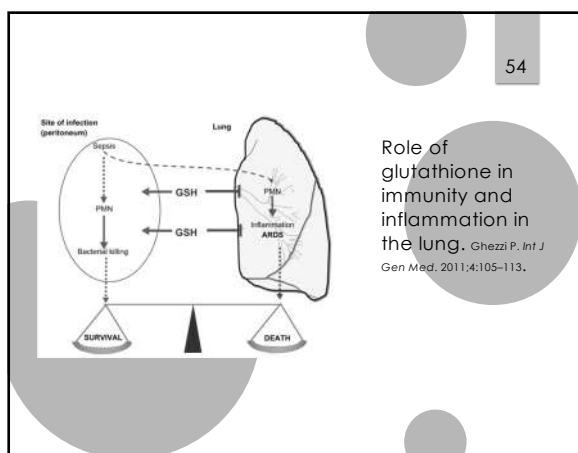
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Glutathione Functions

53

1. Master Antioxidant
2. Reduces Free Radicals
3. Detoxifies Chemicals
4. Chelates Heavy Metals
5. Protects Mitochondrial DNA
6. Cellular Anti-inflammatory compound
7. Storage and transport of cysteine
8. Enhances immune function


53



54

Vitamin C Benefits

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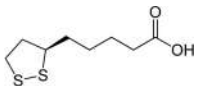


- ▶ Inhibits NLRP inflammasome so decrease IL-1B secretion
- ▶ Silence furins so don't activate virus
- ▶ Powerful Antioxidant
- ▶ Collagen synthesis
- ▶ Carnitine synthesis
- ▶ Important for leukocyte function and immune system
- ▶ Increased absorption of iron

55

Alpha-lipoic Acid Benefits

56




- ▶ Anti-oxidant
- ▶ Amplifies other antioxidants
 - ▶ Glutathione
 - ▶ CoQ10
- ▶ Critical for maintaining optimal blood sugar levels
- ▶ Anti-inflammatory
- ▶ Supports mitochondrial function
- ▶ Neuro-protective
 - ▶ Passes readily into brain & reach all parts of nerve cell

56

Molecular Hydrogen: H₂

57



- ▶ Hydrogen gas is very stable molecule
- ▶ Neutralizes harmful free radicals, including the hydroxyl radical¹
 - ▶ Hydrogen electron donation turns hydroxyl into water
- ▶ Diffuses across membranes, including mitochondria, due to its small size²
 - ▶ Most antioxidant supplements are limited in their cellular distributions and are poorly taken up by organelles like mitochondria³
 - ▶ Hydrogen has the ability to effectively penetrate biomembranes and infiltrate into organelles, such as mitochondria and the nucleus³
 - ▶ In contrast to many antioxidants, H₂ also has the advantage of being able to penetrate the blood-brain barrier³


¹Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Survival* 2002; 14(1): 117-22.
²Molecular hydrogen as a preventive and therapeutic medical gas: Inflation, development and potential of hydrogen medicine. *Oxidative Pharmacology & Therapeutics*. Volume 14, Issue 1, October 2019, Pages 1-11.
³Biological Effects of Hydrogen Administration: From Animal and Human Diseases to Exercise Medicine. *Nickerson G. et al. International Journal of Clinical Medicine*. 2014; 7: 32-74.

57

Molecular Hydrogen: H₂ 58

Summary

- ▶ Anti-oxidant for dangerous hydroxyl radical without destroying free radicals needed for metabolism
- ▶ Activates Nrf2 anti-oxidant cascade including glutathione peroxidase, catalase, and superoxide dismutase (SOD)
- ▶ Decreases pro-inflammatory cytokines through cell signaling
- ▶ Promotes mitochondrial ATP energy function



Molecular hydrogen as a preventive and therapeutic medical gas: Inhibition, development and potential of hydrogen medicine. Gho S. Pharmacology & Therapeutics. Volume 144, Issue 1, October 2014, Pages 1-17.
 Topical Effects of Hydrogen Administration from Anesthetized Human Subjects for Exercise Medicine. Hoshino G, et al. International Journal of Clinical Medicine. 2014, 7, 22-24.

58

Omega-3 Fatty Acids 59

Fabian, CK, Et al. Omega-3 fatty acids for breast cancer prevention and survivorship. Breast cancer research. 2015.

Omega-6

Linoleic Acid (LA) → Arachidonic Acid (AA)

Enzymes: Desaturases, Elongases

Products: Pro-inflammatory Eicosanoids, Prostaglandins, Leukotrienes, Thromboxanes

Omega-3

α-Linolenic Acid (ALA) → Eicosapentaenoic acid (EPA) → Docosahexaenoic acid (DHA)

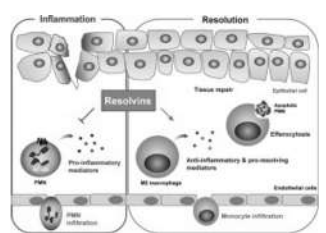
Enzymes: Desaturases, Elongases, Cyclooxygenases, Lipoxygenases

Products: Minimally inflammatory Eicosanoids, Inflammation Resolving: Resolvins, Protectins

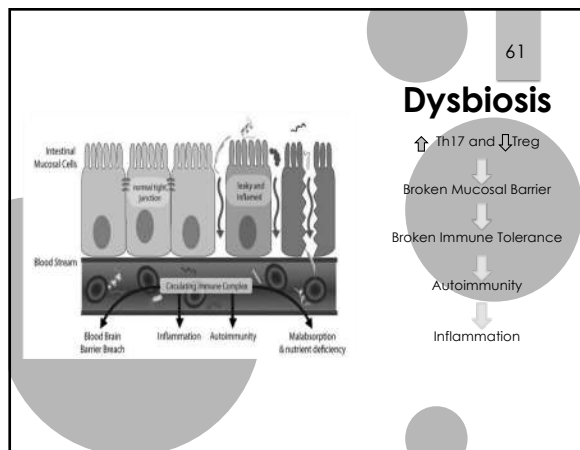
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Resolvins Derived from Omega 3 Fatty Acids 60

Therapeutic potential of resolvins in the prevention and treatment of inflammatory disorders. Ha-Na L. et al. Biochem Pharm. 2012.



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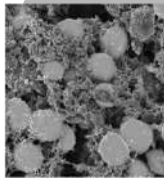
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62

Probiotics: Immune Modulation

Probiotics, Prebiotics and Antibiotics in the Treatment of Inflammatory Bowel Disease.
Calafiore A. et al. Jr. of Gastro and Hep Research. 2012.

Action	Mechanism
Inhibit pathogenic enteric bacteria	Decrease luminal pH Secrete bacteriocidal proteins Colonization resistance Block epithelial binding
Improve epithelial and mucosal barrier function	Produce short-chain fatty acids Enhance mucus production Increase barrier integrity
Alter immunoregulation	Increase IL-10 and TGF- β and decrease TNF- α Increase immunoglobulin A production



IL-1- Interleukin-10; TGF- β Transforming growth factor- β ; TNF: Tumor necrosis factor- α .

62

63

Effect of Probiotics on Alzheimer's Disease

- ▶ 60 Patients with Alzheimer's disease randomized to 30 patients taking probiotics versus 30 patients on placebo for 12 weeks
- ▶ Results: Patients on probiotics
 - ▶ Significant improvement in Mini-mental state exam ($p < 0.0001$)
 - ▶ Decreased plasma malondialdehyde levels,
 - ▶ Decreased CRP
 - ▶ Decreased TG's

▶ Akbari E. et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: A randomized, double-blind controlled trial. Frontiers in Aging Neuroscience. 2016, Volume 8(256).

63

Summary:
Treating
Inflammation


- ▶ Anti-Inflammatory Diet
- ▶ Combination of anti-inflammatory herbs:
 - ▶ Absorption, quality of herbs
- ▶ Anti-oxidants
- ▶ Vitamin and Mineral support

64

64

Dr. Debby Hamilton, MD, MPH

65



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