6th ANNUAL Functional Pharmacy Symposium

FUNCTIONAL MEDICINE Continuing Education

Engineering Immune Protection

Phytonutrients

Lara Zakaria PharmD MS CNs CDN IFMCP

Disclosures

- Nothing to disclose

Objectives

Pharmacist

- Identify the phytonutrients and pathways crucial to immune support
- Review strategies to engineer immune protection with phytonutrients

Technician

- Discuss the impact of phytonutrients on immune health
- Review strategies to support immune protection with phytonutrients

Purpose

What brings you here today?

Phytonutrients

What are they?

Why are they important?

Basic nutrition profile of plants includes:

- Macronutrients
  - Carbohydrates, fiber, fats, and protein
- Micronutrients
  - Vitamins, minerals
  - Some antioxidants
- Phytonutrients
  - Pigments and bioactive compounds
  - Antioxidant function

What are phytochemicals (AKA phytonutrients)?

Naturally occurring compounds in plants

- They contribute to their color, but they're actually part of their defense mechanism
- Postulated that there are tens of thousands of different compounds

These compounds are produced to help them survive

- Through various mechanisms, phytochemicals help the plant resist fungi, bacteria, plant viruses, as well as repel insects and other animals

The more the plant struggles to survive and adapt to its environment, the more potent and complex its phytonutrient composition

- Consider the impact of conventional/modern agriculture on nutrient content

Are organic & regenerative farming practices better?

Why are phytochemicals important?

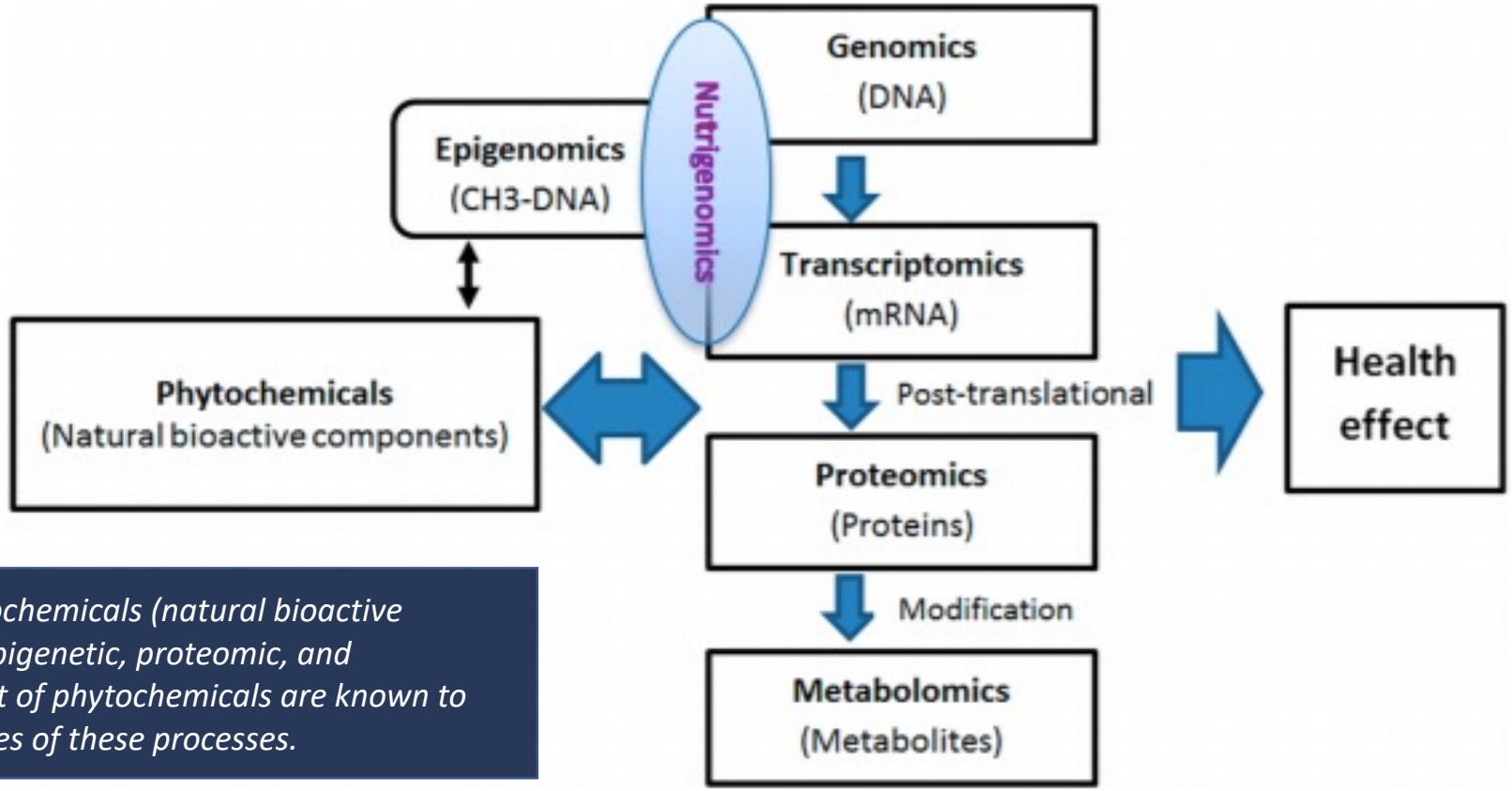


Figure 1. *Influence of phytochemicals (natural bioactive components) on genetic, epigenetic, proteomic, and metabolomic events. A host of phytochemicals are known to influence one or more stages of these processes.*

J Proteome Res. 2013

Phytochemicals sit at the interface of the microbiome, genetics, environment, lifestyle and health outcomes

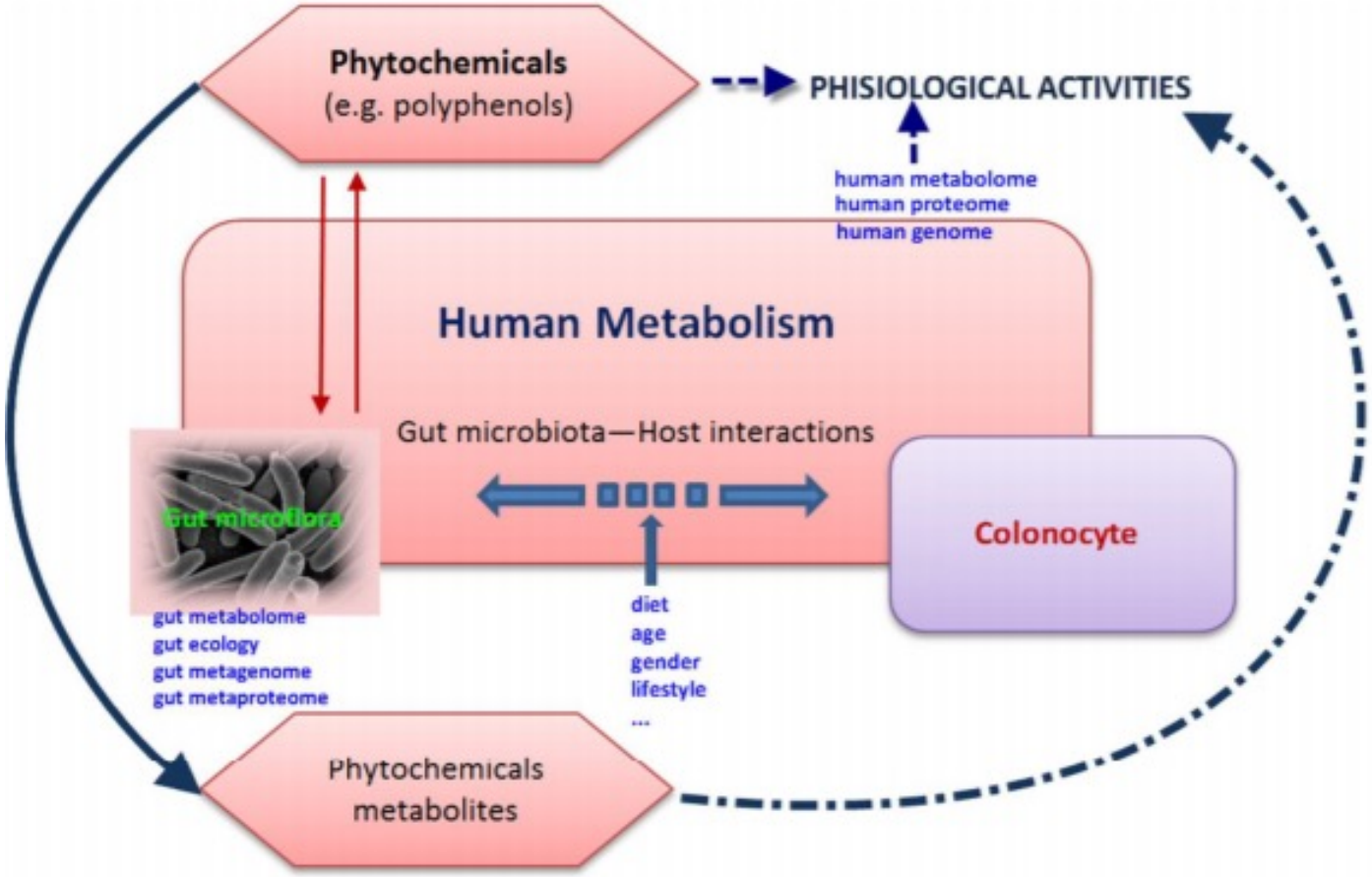
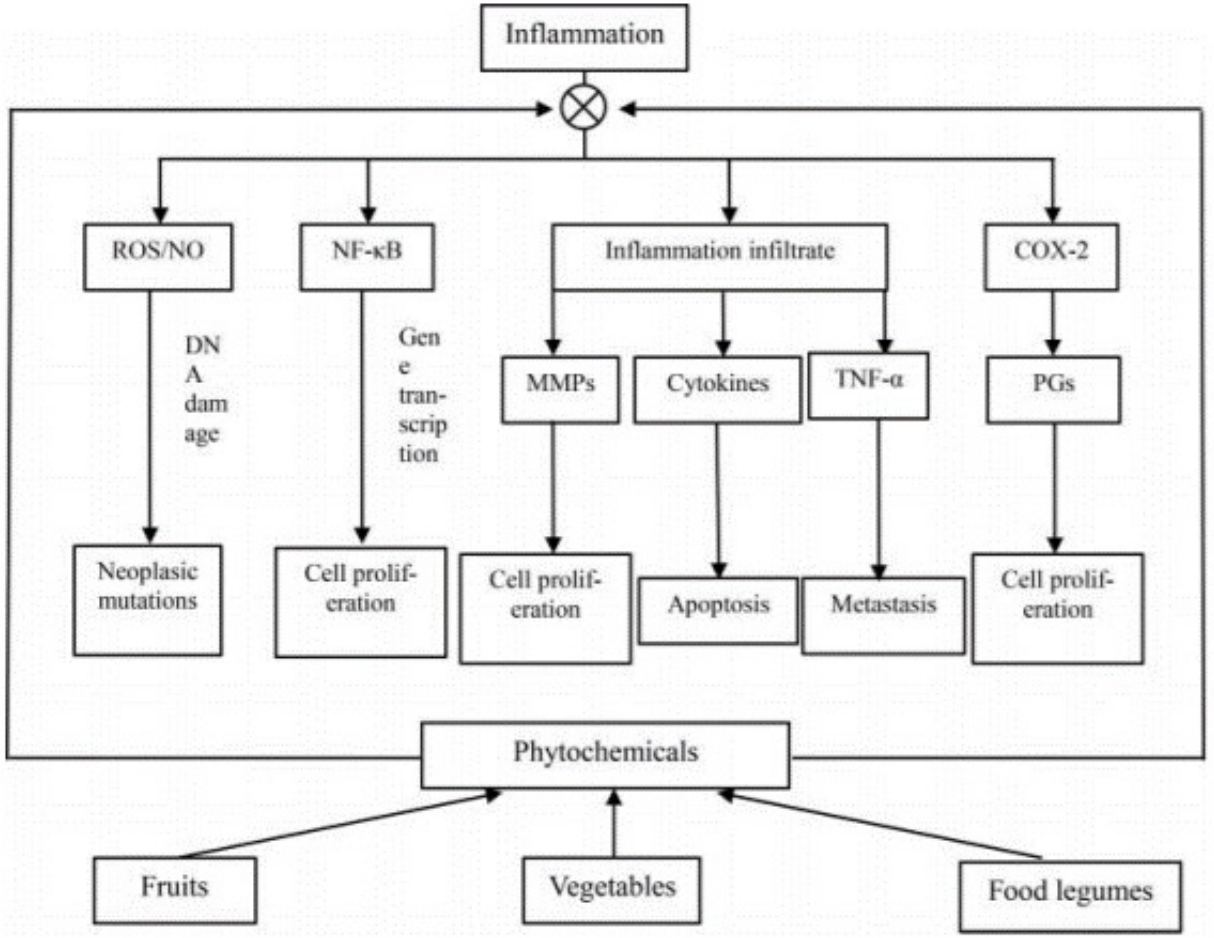


Figure 3. *Interactions between phytochemicals, gut microbiota and host as a combined contribution to human metabolism. The interplay between gut microbiota and host, and its modulation by nutrition, will benefit from the integration of information on a systems biology-wide approach.*

J Proteome Res. 2013

Phytochemicals & Inflammatory Modulation



Crit Rev Food Sci Nutr. 2018

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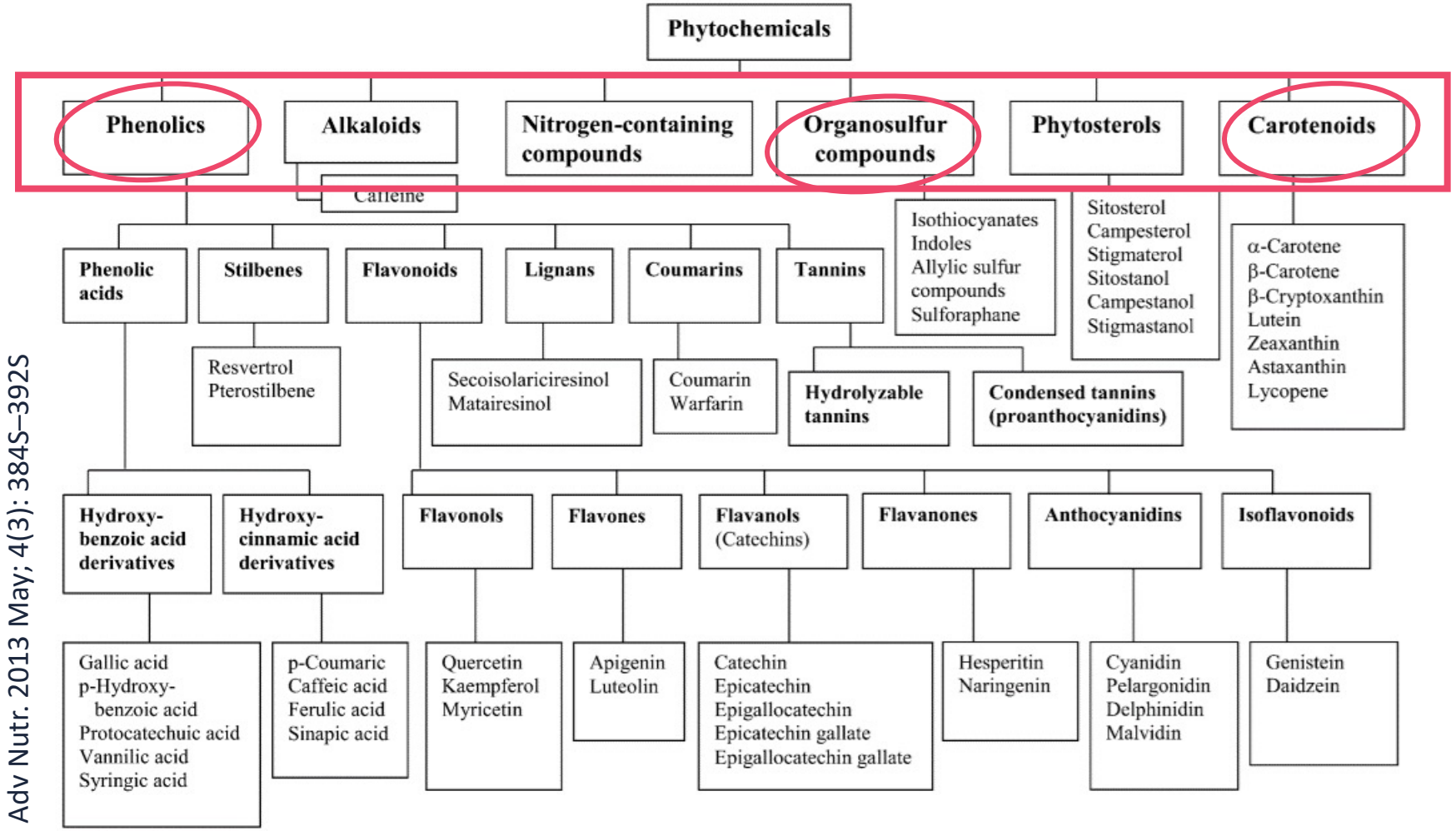
Classification of dietary phytochemicals



Adv Nutr. 2013 May; 4(3): 384S–392S

Biological associations

Inflammaging and metabolic factors

- Low Vit D
- Insulin resistance
- Low omega 3 index
- Altered body composition
- Elevated homocysteine/altered methylation function
- Elevated hsCRP (inflammatory marker)

Oxidative stress

- Antioxidant reserve depletion

Increased Advanced Glycation Endproducts (AGE)

- Increasing HgA1C

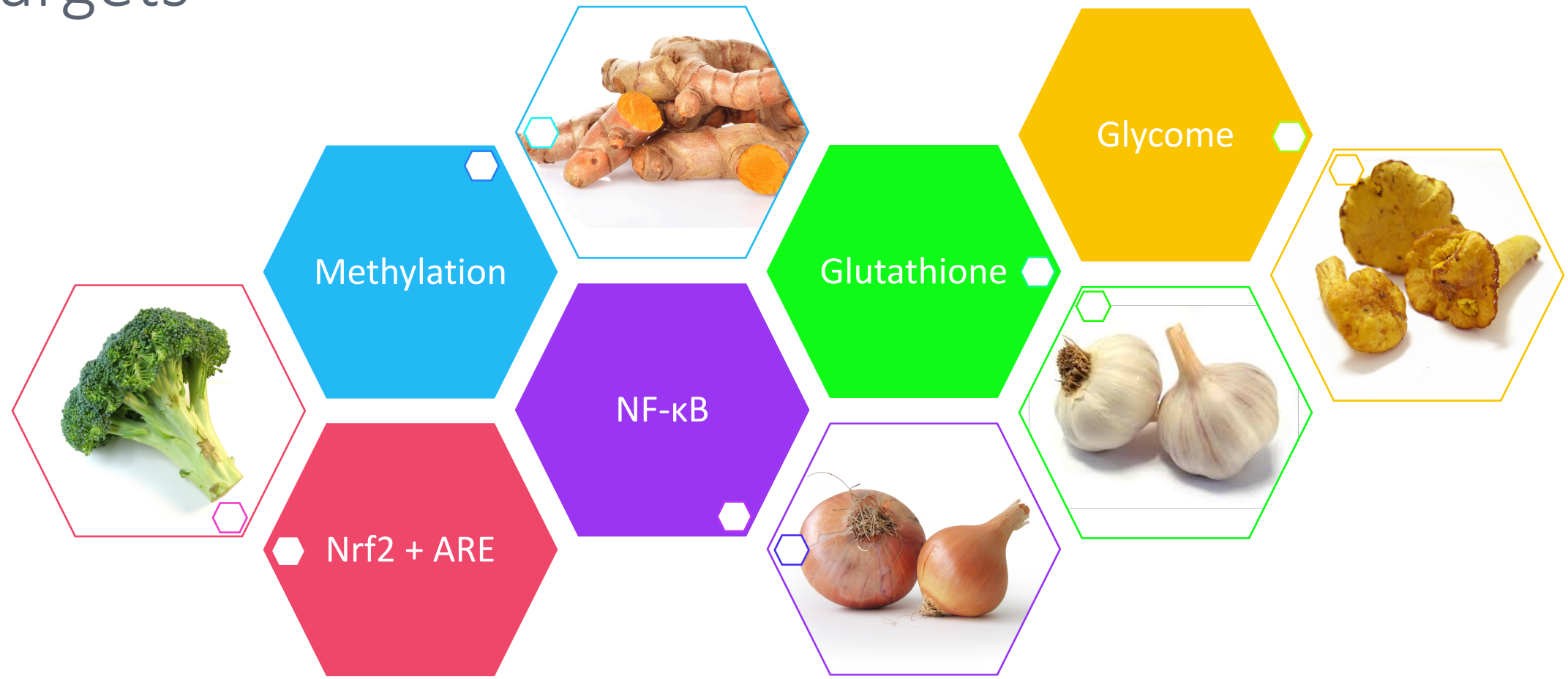
Increased production of autoantibodies

- ANA and various autoimmune process activation

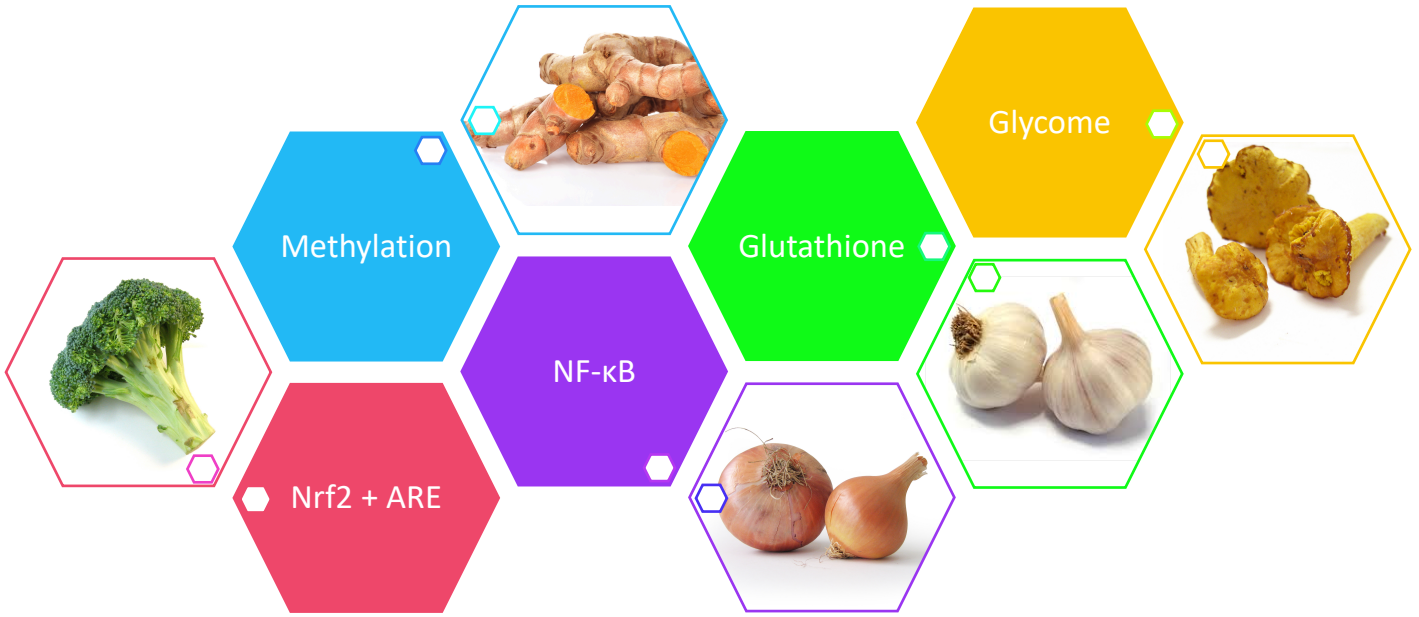
Reduced immune performance

- Reduced WBC count

Targets



Targets



Enhance antioxidant reserve

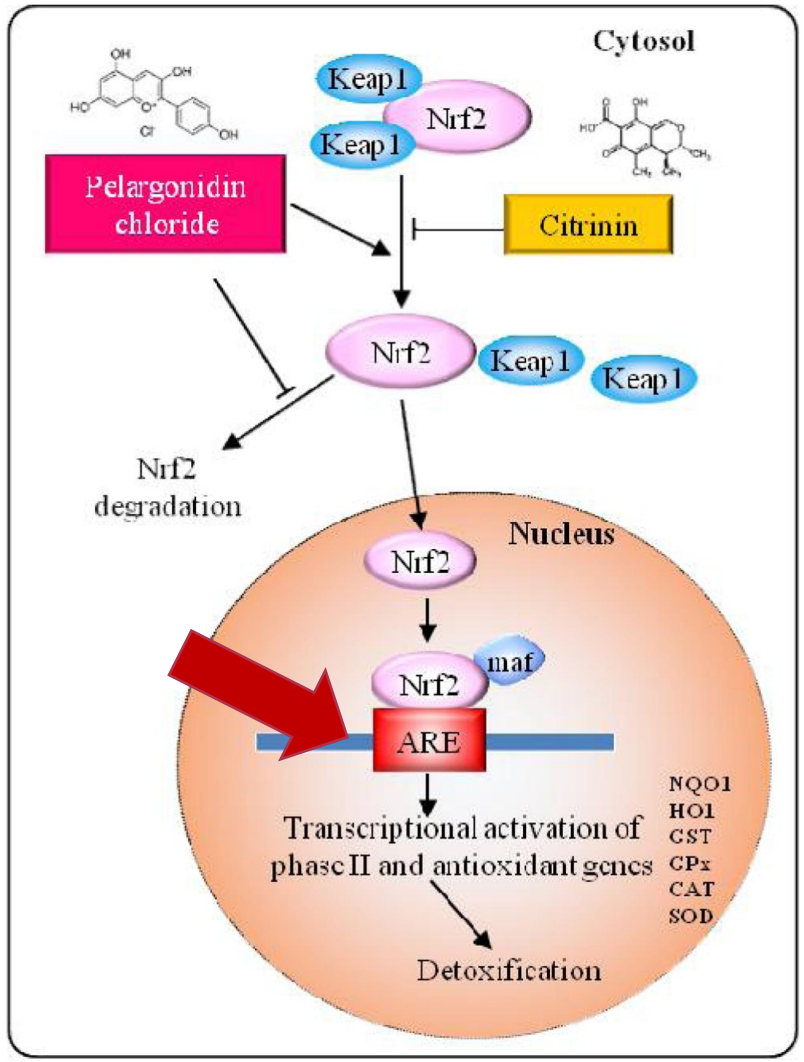
Upregulate capacity to neutralize ROS

Modulate inflammation/immune response

Nrf2 (not Nerf)

Keap1-Nrf2 & ARE*

NRF2 is a transcription factor. In short, it is a protein that when it binds to AREs on a cell's nucleus, it activates certain gene sequences.



**ARE = Antioxidant Response Element*
Front. Pharmacol., 27 November 2017

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Nrf2 has far reaching implications

Since its discovery in 1994, research has revealed Nrf2 to be a crucial regulator of cellular defense mechanisms against xenobiotic and oxidative stress, involving mechanisms such as:

- Glutathione (GSH) and thioredoxin (TXN) antioxidant systems, SOD (superoxide dismutase)
- Phase I and Phase II detoxification enzymes
- Modulation inflammation via NF-κB.
- NADPH regeneration
- Heme metabolism
- Involved with autophagy, intermediary metabolism, stem cell quiescence, and unfolded protein response.
- Affects mitochondrial function, nutrient uptake, and is implicated in a multitude of diseases.

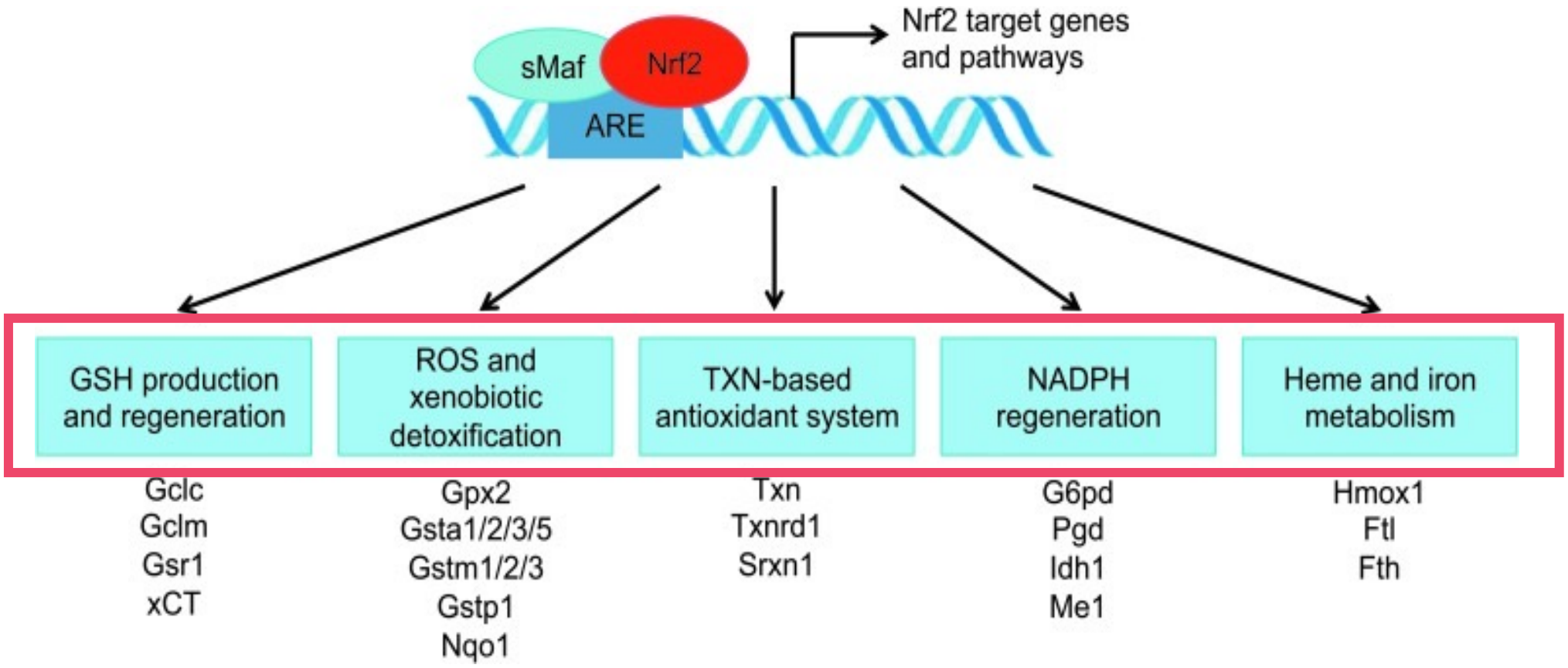
Int J Mol Sci. 2020;21(13):4777
Oxid Med Cell Longev. 2016
Nutr Rev. 2017;75(6):442-455
Oxid Med Cell Longev. 2020

Basically, Nrf2 activation…

Prevents Aging and Disease

Nrf2 can attenuate and minimize many of the chronic stresses that cause illness through damage prevention, damage control, and cellular renewal

The Nrf2-regulated cytoprotective defense system



Antioxid Redox Signal. 2018;29(17):1727-1745

Nrf2: Detoxification & Antioxidant

The Nrf2-mediated signaling pathway protects against environmental insults and endogenous stressors

Oxidative stress is a common status defined as the imbalance between reactive oxygen species (ROS) production and antioxidant capacity in cells

Nrf2 coordinates inducible expression of ARE, influencing various function including antioxidation, anti-inflammation, detoxification enzymes

J Nutr Biochem. 2015;26(12):1401–1413. doi:10.1016/j.jnutbio.2015.08.001
Sheng Li Xue Bao. 2015 Feb 25;67(1):1-18
Oxid Med Cell Longev. 2019;2019:7090534

Review Article

Role of Nrf2 and Its Activators in Respiratory Diseases

Qinmei Liu,[1] Yun Gao,[2] and Xinxin Ci[1]

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Received 26 July 2018; Revised 22 November 2018; Accepted 3 December 2018; Published 8 January 2019

Guest Editor: Luciano Saso

Transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is a major regulator of antioxidant response element- (ARE-) driven cytoprotective protein expression. The activation of Nrf2 signaling plays an essential role in preventing cells and tissues from injury induced by oxidative stress. Under the unstressed conditions, natural inhibitor of Nrf2, Kelch-like ECH-associated protein 1 (Keap1), traps Nrf2 in the cytoplasm and promotes the degradation of Nrf2 by the 26S proteasome. Nevertheless, stresses including highly oxidative microenvironments, impair the ability of Keap1 to target Nrf2 for ubiquitination and degradation, and induce newly synthesized Nrf2 to translocate to the nucleus to bind with ARE. Due to constant exposure to external environments, including diverse pollutants and other oxidants, the redox balance maintained by Nrf2 is fairly important to the airways. To date, researchers have discovered that Nrf2 deletion results in high susceptibility and severity of insults in various models of respiratory diseases, including bronchopulmonary dysplasia (BPD), respiratory infections, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis (IPF), and lung cancer. Conversely, Nrf2 activation confers protective effects on these lung disorders. In the present review, we summarize Nrf2 involvement in the pathogenesis of the above respiratory diseases that have been identified by experimental models and human studies and describe the protective effects of Nrf2 inducers on these diseases.

Dietary Phytochemicals & Nrf2

Sulforophane (cruciferous veggies)

EGCG (Catechins, green tea)

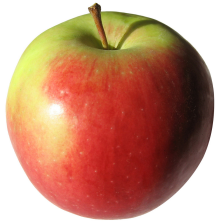
Grape seed

Resveratrol

Curcumin (turmeric)

Pomegranate (ellagitannins)

Cacao (polyphenols)



Quercetin (onions, watercress, apple and others)

Alkyl catechols (Traditionally fermented “ancient” and wood-fire smoked foods)

Crit Rev Food Sci Nutr. 2018;58(8):1260-1270

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Promoting Nrf2

Nutrients that promote Nrf2:

- Phenolic antioxidants
- Vitamin E (gamma- and delta-tocopherols and tocotrienols)
- Omega-3 Fatty Acids (DHA and EPA)
- Vitamin A (Carotenoids, lycopene)
- Isothiocyanates from cruciferous vegetables
- Sulfur compounds from allium and cruciferous vegetables
- Terpenoids (cannabis flowers)

Other Nrf2 promoting factors:

- Low level oxidative stress (hormesis)
- Exercise
- Caloric restriction (IF, FMD, fasting)

J Nutr Biochem. 2015;26(12):1401–1413
Sheng Li Xue Bao. 2015 Feb 25;67(1):1-18

NF-κB Oxidative Stress Transcription Factor

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a transcription factor which regulates the expression of genes involved in immune and inflammatory responses

Oxidative stress production and antioxidant capacity is part of a protective response, however…

Overproduction of ROS plays a role in the pathogenesis of various inflammatory diseases due to imbalanced immune response

Free Radic Biol Med. 2018 Sep;125:3-14

Mediterranean diet and inflammaging within the hormesis paradigm

Morena Martucci,* Rita Ostan,* Fiammetta Biondi, Elena Bellavista, Cristina Fabbri, Claudia Bertarelli, Stefano Salvioli, Miriam Capri, Claudio Franceschi, and Aurelia Santoro

Table 1

Nutritional hormetins of typical Mediterranean foods able to activate specific stress-response pathways

Nutritional hormetin	Food item within traditional Mediterranean diet	Stress pathway
Phytochemicals (phenolic antioxidants, terpenoids, carotenoids, and allium-derived sulfur compounds)	Olives, legumes, leafy green vegetables, tomatoes, eggplant, fruits, garlic, and onion	Activation of nuclear factor erythroid 2 (Nrf2)
Resveratrol	Grapes, red wine	Regulation of redox homeostasis
		Activation of Nrf2 and sirtuin pathway
		Blocking of nuclear factor κB (NF-κB)
Vitamin E	Dried fruits, herbs, leafy green vegetables	Activation of heat shock response
		Down-regulation of NF-κB
n-3 polyunsaturated fatty acids	Fish, nuts	Activation of Nrf2
		Blocking of NF-κB
Fiber	Legumes, unrefined whole-grain cereals, fresh vegetables, fruits	Cooperation with cellular stress pathways (heat shock proteins)

Nutr Rev. 2017;75(6):442-455

molecules

MDPI

Review

Review of Functional and Pharmacological Activities of Berries

Oksana Golovinskaia and Chin-Kun Wang *

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Abstract: Functional plant-based foods (such as fruits, vegetables, and berries) can improve health, have a preventive effect, and diminish the risk of different chronic diseases during in vivo and in vitro studies. Berries contain many phytochemicals, fibers, vitamins, and minerals. The primary phytochemicals in berry fruits are phenolic compounds including flavonoids (anthocyanins, flavonols, flavones, flavanols, flavanones, and isoflavonoids), tannins, and phenolic acids. Since berries have a high concentration of polyphenols, it is possible to u
diseases pharmacologically by acting on oxidative stress and inflan
leading causes of diabetes, neurological, cardiovascular diseases, and
commonly consumed berries: blackberries, blackcurrants, blueberries,
raspberries, and strawberries and their polyphenols as potential medici
of pharmacologically active compounds) in the treatment of diabetes,
other diseases. Moreover, much attention is paid to the bioavailability
Hence, this comprehensive review shows that berries and their bioactive compounds possess medicinal properties and have therapeutic potential. Nevertheless, future clinical trials are required to study and improve the bioavailability of berries' phenolic compounds and extend the evidence that the active compounds of berries can be used as medicinal foods against various diseases.

Conclusion: *The interaction between berry phenolics and the microbiota plays an essential role in berry phenolics bioavailability and contributes to gut health.*

Important Antioxidant Compounds

Major antioxidants
• Ascorbate (vitamin C) • Vitamin E • Vitamin A/β-carotene • Riboflavin • Selenium • Zinc • Copper • Manganese • Glutathione • Isoflavones

Building blocks or cofactors
• Glycine, Mg (glutathione building block) • Selenium, copper, zinc (glutathione peroxidase) • Riboflavin (glutathione reductase) • Copper, Zinc, Manganese (SOD)

Vitamin C

Vitamin C is an essential nutrient

Powerful mast cell stabilizer → antihistamine activity (doses as high as 2g/day)

Once of Vit C's roles is immune regulation and inflammasome mediator

Vitamin C has been shown to have an inhibitory effect on the activation of the **NLRP3 inflammasome** in vitro and in vivo

Mechanistically, this inhibition is via scavenging mitochondrial ROS

Inflammasome. 2.10.1515/infl-2016-0001

Quercetin

Pharmacological studies have shown that quercetin and galangin exhibit anti-inflammatory efficacy *in vitro* and *in vivo* might show benefit in management of **atopic dermatitis**. Effects may also be amplified by DHA

- Int J Mol Med. 2018 Feb;41(2):888-898
- Mol Med Rep. 2016 Jul;14(1):499-508

Quercetin has been shown to have a **bronchodilation** effect

- Sci Rep. 2018 Feb 15;8(1):3114

Quercetin has significant effectiveness as a **mast cell inhibitor** for allergic and inflammatory diseases, and may actually outperform cromolyn

- PLoS One. 2012;7(3):e33805

frontiers in Immunology

REVIEW
published: 19 June 2020
doi: 10.3389/fimmu.2020.01451

Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19)

Ruben Manuel Luciano Colunga Biancatelli[1,2,3*], *Max Berrill*[4], *John D. Catravas*[1,2,5] *and Paul E. Marik*[1]

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) represents an emergent global threat which is straining worldwide healthcare capacity. As of May 27th, the disease caused by SARS-CoV-2 (COVID-19) has resulted in more than 340,000 deaths worldwide, with 100,000 deaths in the US alone. It is imperative to study and develop pharmacological treatments suitable for the prevention and treatment of COVID-19. Ascorbic acid is a crucial vitamin necessary for the correct functioning of the immune system. It plays a role in stress response and has shown promising results when administered to the critically ill. Quercetin is a well-known flavonoid whose antiviral properties have been investigated in numerous studies. There is evidence that vitamin C and quercetin co-administration exerts a synergistic antiviral action due to overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin, increasing its efficacy. Safe, cheap interventions which have a sound biological rationale should be prioritized for experimental use in the current context of a global health pandemic. We present the current evidence for the use of vitamin C and quercetin both for prophylaxis in high-risk populations and for the treatment of COVID-19 patients as an adjunct to promising pharmacological agents such as Remdesivir or convalescent plasma.

There is evidence that vitamin C and quercetin co-administration exerts a synergistic antiviral action due to overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin, increasing its efficacy.

Front Immunol. 2020;11:1451

Curcumin *(Curcuma longa)*

Inhibits the activation of free radical activated transcription factors such as NFκβ and nitric oxide synthase

Nrf2 activator and antioxidant pathways

It also modulates the proinflammatory cytokines and anti-inflammatory process including T-reg cells

Activity on Cyclooxygenase (COX) and Lipoxygenase (LOX) inflammatory mechanisms

Epigenetic modulator of methylation (phase II detoxification)

Front Genet. 2019;10:514
Curr Mol Med. 2020;20(2):116-133
Arthritis Res Ther. 2008;10(4):R85
Crit Rev Food Sci Nutr. 2019;59(1):89-101

Resveratrol *(3,5,4'-trihydroxystilbene)*

Enhances T-regs response which can dampen Th2-driven inflammatory response in asthma (via FOXP3)

Favorable modulation of virus-induced response activation via NLRP3 inflammasome activation

Mitigates pathogenesis of SARS-CoV2 via RAS and ACE2 expression

Balancing immune response by stimulation of immune response (notably CTL and NK cells) and downregulation of cytokines.

Front Immunol. 2018 Dec 20;9:2992
Acta Virol. 2020;64(3):276-280

Epigallocatechin gallate (EGCG)

Epigallocatechin gallate (EGCG) is a flavanol/catechin found in high concentrations in green tea, as well as other tea varieties and fruits like cranberries, strawberries, blackberries, avocado and apple.

Favorable modulation of virus-induced pathology via NLRP3 inflammasome pathway activation

Nrf2 reduces angiotensin-converting enzyme 2 (ACE2) receptors expression in respiratory epithelial cells.

225 mg daily of extract OR 3-4 cups of green tea daily

Antioxidants (Basel). 2020;9(8):659

antioxidants

MDPI

Hypothesis

Flavonoids Activation of the Transcription Factor Nrf2 as a Hypothesis Approach for the Prevention and Modulation of SARS-CoV-2 Infection Severity

Patricia Mendonca and Karam F. A. Soliman *

College of Pharmacy and Pharmaceutical Sciences, Florida
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SARS-CoV2 inflammatory process, and oxidative stress of the epithelium lining cells activate the transcription factor Nrf2 for protection.

Nrf2 reduces ACE2 receptors expression in respiratory epithelial cells.

Disease severity may also be modulated by comorbidity including immune response, obesity, and age, where decreased level of Nrf2 are common.

Nrf2 activators enhance antiviral mediators' expression priming cells against viral infection

Hypothesis paper describes the use of flavonoid supplements combined with vitamin D3 to activate Nrf2, which may be a potential target to prevent and/or decrease SARS-CoV-2 infection severity, reducing oxidative stress and inflammation, enhancing innate immunity, and downregulating ACE2 receptors.

Antioxidants (Basel). 2020;9(8):659

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German Edition: doi.org/10.1002/ange.202011015

Structural Characterization of N-Linked Glycans in the Receptor Binding Domain of the SARS-CoV-2 Spike Protein and their Interactions with Human Lectins

Maria Pia Lenza, Iker Oyenarte, Tammo Diercks, Jon Imanol Quintana, Ana Gimeno, Helena Coelho, Ana Diniz, Francesca Peccati, Sandra Delgado, Alexandre Bosch, Mikel Valle, Oscar Millet, Nicola G. A. Abrescia, Asís Palazón, Filipa Marcelo, Gonzalo Jiménez-Osés, Jesús Jiménez-Barbero, Ana Ardá,* and June Ereño-Orbea**

Dedicated to Professor Christian Griesinger on the occasion of his 60th birthday

Abstract: *The glycan structures of the receptor binding domain of the SARS-CoV2 spike glycoprotein expressed in human HEK293F cells have been studied by using NMR. The different possible interacting epitopes have been deeply analysed and characterized, providing evidence of the presence of glycan structures not found in previous MS-based analyses. The interaction of the RBD ^{13}C-labelled glycans with different human lectins, which are expressed in different organs and tissues that may be affected during the infection process, has also been evaluated by NMR. In particular, ^{15}N-labelled galectins (galectins-3, -7 and -8 N-terminal), Siglecs (Siglec-8, Siglec-10), and C-type lectins (DC-SIGN, MGL) have been employed. Complementary experiments from the glycoprotein perspective or from the lectin's point of view have permitted to disentangle the specific interacting epitopes in each case. Based on these findings, 3D models of the interacting complexes have been proposed.*

Angew Chem Int Ed Engl. 2020;59(52):23763-23771

- Glycans are involved in a range of pathologic and pathogenic processes including metabolic diseases, cancer, and host–pathogen interactions
- Play a significant role in coagulation response
- ACE2 receptors are glycated
- Authors suggest a lectin-mediated molecular pathways that may contribute to viral infection and immune exacerbation

Modulating Immune Function

- Diet & nutrients
- Lifestyle
- Herbals & nutraceuticals
- Homeopathy
- Acupuncture
- HPA axis support/stress management

Thank You!

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