2022-9 Nrf2 Activators and Covid-19

Both Adaptogens and and some polyphenols can activate the nuclear factor erythroid-2-related factor 2 (Nrf2) pathway, For example, Amla, Emblica *officinalis,* is an adaptogen that activates the Nrf2 pathway. The pathway removes cellular trash, misfolded proteins, both organic and inorganic xenobiotics, such as parts of viruses and toxic metals. It fixes or restores you energy producing mitochondria and restore life to cells by activating telomerase to lengthen their telomeres. It makes you fell young again. Adaptogens help with mental and physical stress. A regular diet of adaptogens can enable rats and people to swim twice as long before they drown. Adaptogens help recovery from any sickness.

Antiviral

Review
Pharmaceuticals (Basel)
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The Role of Adaptogens in Prophylaxis and Treatment of Viral Respiratory Infections

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Abstract

The aim of our review is to demonstrate the potential of herbal preparations, specifically adaptogens for prevention and treatment of respiratory infections, as well as convalescence, specifically through supporting a challenged immune system, increasing resistance to viral infection, inhibiting severe inflammatory progression, and driving effective recovery. The evidence from pre-clinical and clinical studies with *Andrographis paniculata*, *Eleutherococcus senticosus*, *Glycyrrhiza* spp., *Panax* spp., *Rhodiola rosea*, *Schisandra chinensis*, ***Withania somnifera***, their combination products and melatonin suggests that **adaptogens can be useful in prophylaxis and treatment of viral infections at all stages of progression of inflammation as well as in aiding recovery of the organism by (i) modulating innate and adaptive immunity, (ii) anti-inflammatory activity, (iii) detoxification and repair of oxidative stress-induced damage in compromised cells, (iv) direct antiviral effects of inhibiting viral docking or replication, and (v) improving quality of life during convalescence.**

Keywords: Andrographis; Eleutherococcus; Glycyrrhiza; Panax; Rhodiola; Schisandra; Withania; adaptogens; melatonin; viral infection.

Conflict of interest statement

The authors declare no conflict of interest.

Sheng Li Xue Bao

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

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

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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 health-span 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.

Dr. Bill's summary:
Amla causes the transcription factor Nrf2, nuclear factor erythroid-2-related factor 2, to activates the transcription of over 500 genes, witch is almost 4% of the estimated 25,000 human genes. This cause cells to produce hundreds of enzymes with cytoprotective functions. Raising Nrf2 has been found to prevent and/or treat a large number of chronic inflammatory diseases. Currently drug companies are trying to produce drugs that can do what Amla can do to the structure and function of cells.

Review
Trends Food Sci Technol
actions:
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Potential protective mechanisms of green tea polyphenol EGCG against COVID-19

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Free PMC article
Full text links Cite

Abstract
Background: The world is in the midst of the COVID-19 pandemic. In this comprehensive review, we discuss the potential protective effects of (-)-epigallocatechin-3-gallate (EGCG), a major constituent of green tea, against COVID-19.
Scope and approach: Information from literature of clinical symptoms and molecular pathology of COVID-19 as well as relevant publications in which EGCG shows potential protective activities against COVID-19 is integrated and evaluated.

Key findings and conclusions: EGCG, via activating Nrf2, can suppress ACE2 (a cellular receptor for SARS-CoV-2) and TMPRSS2, which mediate cell entry of the virus. Through inhibition of SARS-CoV-2 main protease, EGCG may inhibit viral reproduction. EGCG via its broad antioxidant activity may protect against SARS-CoV-2 evoked mitochondrial ROS (which promote SARS-CoV-2 replication) and against ROS burst inflicted by neutrophil extracellular traps. By suppressing ER-resident GRP78 activity and expression, EGCG can potentially inhibit SARS-CoV-2 life cycle. EGCG also shows protective effects against 1) cytokine storm-associated acute lung injury/acute respiratory distress syndrome, 2) thrombosis via suppressing tissue factors and activating platelets, 3) sepsis by inactivating redox-sensitive HMGB1, and 4) lung fibrosis through augmenting Nrf2 and suppressing NF-κB. These activities remain to be further substantiated in animals and humans. The possible concerted actions of EGCG suggest the importance of further studies on the prevention and treatment of COVID-19 in humans. These results also call for epidemiological studies on potential preventive effects of green tea drinking on COVID-19.
Keywords: COVID-19; EGCG; Prevention; SARS-CoV-2; Tea; Treatment.
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Conflict of interest statement
The authors declare no conflict of interest.

Review
Trends Pharmacol Sci
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Can Activation of NRF2 Be a Strategy against COVID-19?

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Abstract

Acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 is largely the result of a dysregulated host response, followed by damage to alveolar cells and lung fibrosis. Exacerbated proinflammatory cytokines release (cytokine storm) and loss of T lymphocytes (leukopenia) characterize the most aggressive presentation. We propose that a multifaceted anti-inflammatory strategy based on pharmacological activation of nuclear factor erythroid 2 p45-related factor 2 (NRF2) can be deployed against the virus. **The strategy provides robust cytoprotection by restoring redox and protein homeostasis, promoting resolution of inflammation, and facilitating repair. NRF2 activators such as sulforaphane and bardoxolone methyl are already in clinical trials. The safety and efficacy information of these modulators in humans, together with their well-documented cytoprotective and anti-inflammatory effects in preclinical models, highlight the potential of this armamentarium for deployment to the battlefield against COVID-19.**

Keywords: KEAP1; SARS-CoV-2; anti-inflammatory ARDS; bardoxolone methyl; sulforaphane.

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Review

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Nrf2 Activator PB125® as a Carnosic Acid-Based Therapeutic Agent against Respiratory Viral Diseases, including COVID-19

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Full text links Cite
Abstract
PB125® is a phytochemical composition providing potent Nrf2 activation as well as a number of direct actions that do not involve Nrf2. Nrf2 is a transcription actor that helps maintain metabolic balance by providing redox-sensitive expression of numerous genes controlling normal day-to-day metabolic pathways. When ordinary metabolism is upset by extraordinary events such as injury, pathogenic infection, air or water pollution, ingestion of toxins, or simply by the slow but incessant changes brought about by aging and genetic variations, Nrf2 may also be called into action by the redox changes resulting from these events, whether acute or chronic. A complicating factor in all of this is that Nrf2 levels decline with aging, leaving the elderly less able to maintain proper redox balance. The dysregulated gene expression that results can cause or exacerbate a wide variety of pathological conditions, including susceptibility to viral infections. **This review examines the characteristics desirable in Nrf2 activators that have therapeutic potential, as well as some of the patterns of dysregulated gene expression commonly observed during pulmonary infections and the normalizing effects possible by judicious use of phytochemicals to increase the activation level of available Nrf2.**
Keywords: COVID-19; Nrf2; PB125; SARS-CoV-2; carnosic acid; coronavirus; cytokines; endothelium; interferon.
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SARS-CoV2-mediated suppression of NRF2-signaling reveals potent antiviral and anti-inflammatory activity of 4-octyl-itaconate and dimethyl fumarate

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  PMID: 33087717 **Free PMC article.**

Abstract

Antiviral strategies to inhibit Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) and the pathogenic consequences of COVID-19 are urgently required. Here, we demonstrate that the NRF2 antioxidant gene expression pathway is suppressed in biopsies obtained from COVID-19 patients. Further, we uncover that NRF2 agonists 4-octyl-itaconate (4-OI) and the clinically approved dimethyl

fumarate (DMF) induce a cellular antiviral program that potently inhibits replication of SARS-CoV2 across cell lines. The inhibitory effect of 4-OI and DMF extends to the replication of several other pathogenic viruses including Herpes Simplex Virus-1 and-2, Vaccinia virus, and Zika virus through a type I interferon (IFN)-independent mechanism. In addition, 4-OI and DMF limit host inflammatory responses to SARS-CoV2 infection associated with airway COVID-19 pathology. In conclusion, **NRF2 agonists 4-OI and DMF induce a distinct IFN-independent antiviral program that is broadly effective in limiting virus replication and in suppressing the pro-inflammatory responses of human pathogenic viruses, including SARS-CoV2.**

Conflict of interest statement

The authors declare no competing interests.

Most of the good phenols have been removed from the food we eat today.

Am J Clin Nutr
actions
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Bitter taste, phytonutrients, and the consumer: a review

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Full text links Cite

Abstract

Dietary phytonutrients found in vegetables and fruit appear to lower the risk of cancer and cardiovascular disease. Studies on the mechanisms of chemoprotection have focused on the biological activity of plant-based phenols and polyphenols, flavonoids, isoflavones, terpenes, and glucosinolates. Enhancing the

phytonutrient content of plant foods through selective breeding or genetic improvement is a potent dietary option for disease prevention. However, most, if not all, of these bioactive compounds are bitter, acrid, or astringent and therefore aversive to the consumer. Some have long been viewed as plant-based toxins. As a result, the food industry routinely removes these compounds from plant foods through selective breeding and a variety of debittering processes. This poses a dilemma for the designers of functional foods because increasing the content of bitter phytonutrients for health may be wholly incompatible with consumer acceptance. Studies on phytonutrients and health ought to take sensory factors and food preferences into account.