

REVIEW OF EMERGING RESEARCH

Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery

Yanuck SF¹, Pizzorno J², Messier H³, Fitzgerald KN⁴

¹Program on Integrative Medicine, Department of Physical Medicine and Rehabilitation, University of North Carolina School of Medicine; Yanuck Center for Life & Health; Cogence Immunology; Chapel Hill, NC, USA. Corresponding author: yanuck@yanuckcenter.com

²Editor-in-Chief, Integrative Medicine, A Clinicians Journal; Coauthor, Textbook of Natural Medicine; Chair, Board of Directors, Institute for Functional Medicine; Founding President, Bastyr University; Seattle, WA, USA.

³Medical Director, Altum Medical; Chief Medical Officer, Medical Intelligence Learning Labs; San Francisco, CA, USA.

⁴Clinic Director, Sandy Hook Functional Medicine; Sandy Hook, CT, USA.

Abstract

This paper presents an evidence-based strategy for improving clinical outcomes in COVID-19. Recommendations are based on the phases of the disease, because optimal interventions for one phase may not be appropriate for a different phase. The four phases addressed are: Prevention, Infection, Inflammation and Recovery.

Underlying this phased approach is recognition of emerging evidence for two different components of pathophysiology, early infection and late stage severe complications. These two aspects of the disease suggest two different patterns of clinical emphasis that seem on the surface to be not entirely concordant. We describe the application of therapeutic strategies and appropriate tactics that address four main stages of disease progression for COVID-19.

Emerging evidence in COVID-19 suggests that the SARS-CoV-2 virus may both evade the innate immune response and kill macrophages. Delayed innate immune response and a depleted population of macrophages can theoretically result in a blunted antigen presentation, delaying and diminishing activation of the adaptive immune response. Thus, one clinical strategy involves supporting patient innate and adaptive immune responses early in the time course of illness, with the goal of

improving the timeliness, readiness, and robustness of both the innate and adaptive immune responses.

At the other end of the disease pathology spectrum, risk of fatality in COVID-19 is driven by excessive and persistent upregulation of inflammatory mechanisms associated with cytokine storm. Thus, the second clinical strategy is to prevent or mitigate excessive inflammatory response to prevent the cytokine storm associated with high mortality risk.

Clinical support for immune system pathogen clearance mechanisms involves obligate activation of immune response components that are inherently inflammatory. This puts the goals of the first clinical strategy (immune activation) potentially at odds with the goals of the second strategy (mitigation of proinflammatory effects). This creates a need for discernment about the time course of the illness and with that, understanding of which components of an overall strategy to apply at each phase of the time course of the illness.

We review evidence from early observational studies and the existing literature on both outcomes and mechanisms of disease, to inform a phased approach to support the patient at risk for infection, with infection, with escalating inflammation during infection, and at risk of negative sequelae as they move into recovery.

Contents

Summary	9
Immunological Framework	10
Clinical Strategy for Patient Support in COVID-19	13
Four Phases in the Time Course of COVID-19	13
Five Targets of Support	14
Tactics to Support the Clinical Strategy	19
Assessment of Risk Factors	19
Tactics for the Five Targets of Support	19
1. Foundational Support	19
2. Natural Killer (NK) cell support	23
3. Th1 cell support	23
4. Anti-Inflammatory Support	25
5. Anti-Oxidant Support	26
Appendix I - Drug – Nutrient Interactions	28
References	29

Summary

Four Phases of COVID-19

Clinicians will encounter patients in one of four phases of COVID-19, each requiring its own focus.

- Prevention - support is focused on immune surveillance efficiency and reduction of baseline levels of inflammation, to improve outcomes if the patient becomes infected,
- Infection - support emphasizes immune activity against infection,
- Escalating Inflammation - support is focused on anti-inflammatory measures, and
- Recovery - support is focused on resolving inflammation, inhibiting fibrosis and other forms of tissue damage, curtailing losses of function, and restoring and reoptimizing function. Because patients have been observed to relapse into the Escalating Inflammation Phase, it is essential for clinical surveillance to continue well into what may appear to be the Recovery Phase.

Determination of the proper clinical targets (the strategy) and assessment of the merits of tools to address those targets (the tactics) are critical for optimizing clinical outcomes. In each of the four phases of COVID-19,

knowledge of the underlying immunology should inform the clinician's strategy and tactics. It is therefore essential that the clinician understand the underlying immunology that informs clinical decisions in order to react appropriately to the unfolding clinical course.

Five Targets of Support are presented in this paper. The following table summarizes the five Targets of Support (rows) that function across four Phases of COVID-19 (the columns). These Phases and Targets, and the knowledge that undergirds them, can be used to form an optimized clinical approach to patient care. The first table describes the basic structure. The second populates that structure with specific tactics. We encourage the reader to read the paper in full, rather than only using the tables.

The following table summarizes the main features of the clinical strategies and tactics outlined in this paper. Clinicians are cautioned to apply these approaches in the context of ongoing discernment as to the patient's unfolding case and to make course corrections as necessary, as is inherent to the nature of clinical practice. In particular, it is essential for those clinicians who have been accustomed to working with patients whose illnesses are chronic to recognize the inherently different pattern and process of acute illness, and have a low threshold for seeking acute care support.

Figure 1. Five Targets of Support as they apply to the four Phases in the time course of disease. It's essential that if the patient moves from the Infection Phase to the Escalating Inflammation Phase, the emphasis shifts to downregulation of the potentially life-threatening inflammatory process.

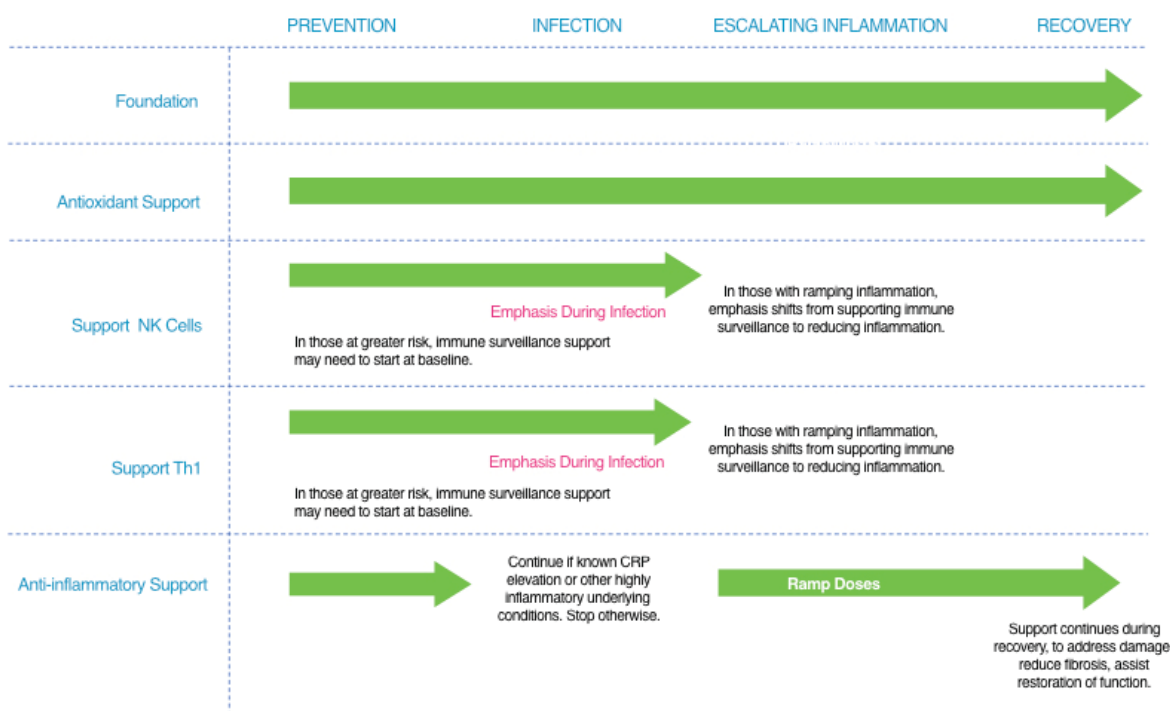
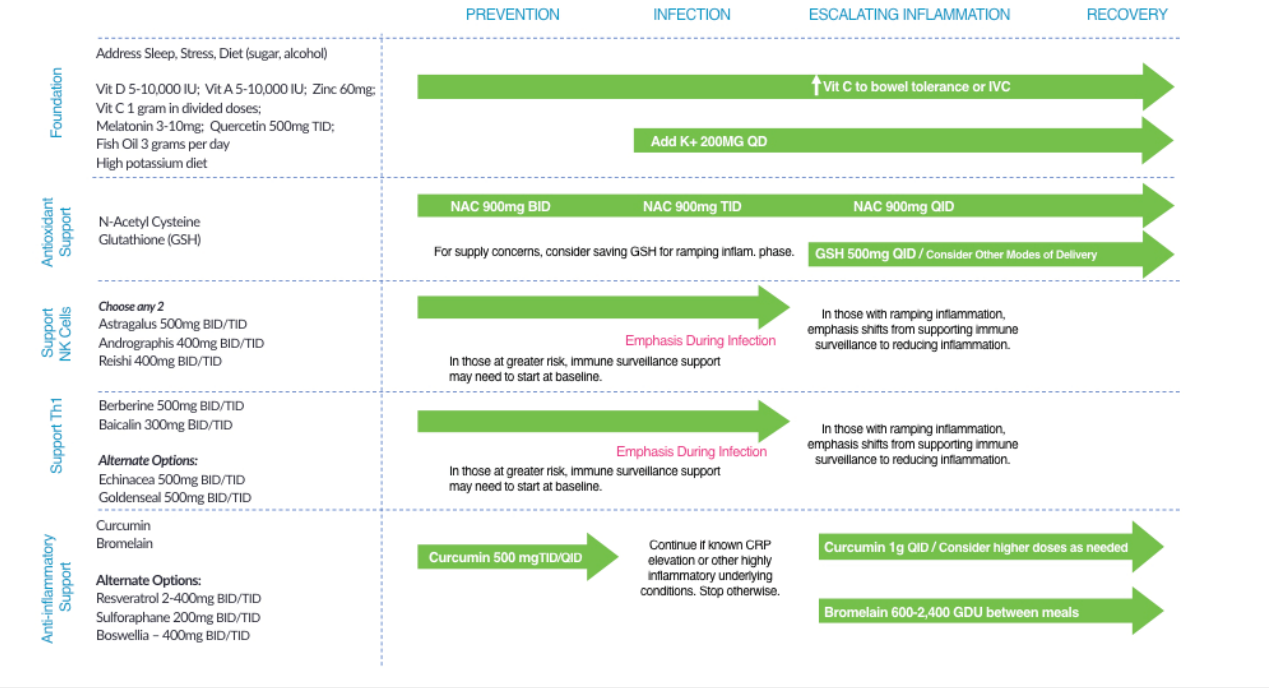


Figure 2. Proposed approach to populating the five Targets of Support, across the four Phases of COVID-19 disease.



Immunological Framework

Emerging evidence in COVID-19 suggests that the SARS-CoV-2 virus employs pathogen evasion strategies against macrophages, including delaying macrophage activation and infecting and killing macrophages.¹ The capacity to delay the innate immune response is consistent with the observation that host infection can occur two to fourteen days before the onset of symptoms. In a prospective examination of patients stratified according to percentage of total lymphocytes (without differentiation of constituent cells), those with the most marked lymphopenia (<5%) had significantly higher mortality than those with total lymphocytes <20%, measured at two time points.² Lymphopenia linked to mortality implies that macrophages and dendritic cells (DC's) are failing to respond to epithelial cell-derived pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) and hence achieve optimal maturation in order to recognize and ultimately present antigen to naïve T cells, in order to engage the adaptive immune system. Failure of clonal expansion of adaptive immune cells is a driver of lymphopenia. The weakness of the initial round of immune response may also make it more likely that when the clonally expanded populations of T and B cells undergo subsequent timed clonal contraction, there may often still be enough virus left for a surge of disease symptoms in the so-called second wave of illness.

SARS-CoV-2 has also been shown to infect but not replicate in MT-2 experimental T cells in a lab setting.³ A study of Middle Eastern Respiratory Syndrome (MERS) showed that the MERS coronavirus induced apoptosis

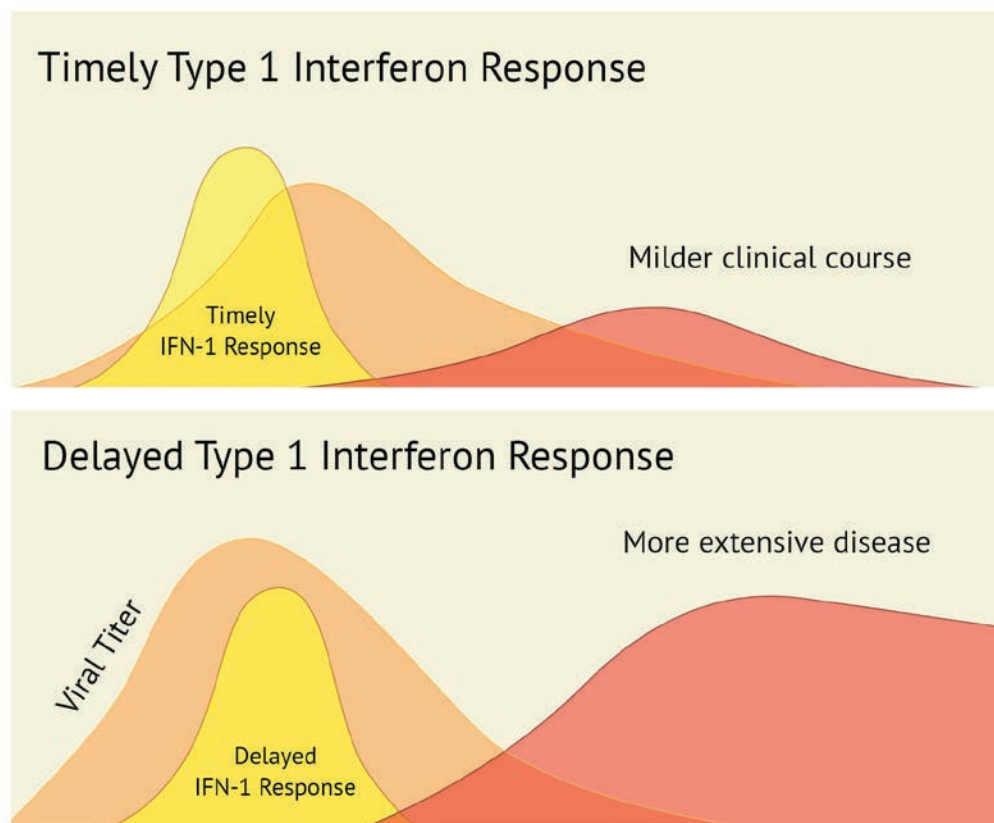
(programmed cell death) in the infected T cells.⁴ In a SARS-CoV-1 experimental model, robust virus replication was accompanied by delayed type I interferon (IFN-I) signaling, yielding inflammatory responses and lung immunopathology that diminished survival. Early IFN-I administration ameliorated immunopathology, suggesting that supporting efficient immune response early in the infectious process might be useful.⁵

In SARS-CoV-2 infection, if macrophages and DCs are being destroyed by the virus before they can initiate effective antigen presentation to activate the adaptive immune system, those with the highest viral loads might be expected to do most poorly. Higher viral loads would be expected to destroy more macrophages and DCs and to more decisively inhibit the immune activation necessary to get ahead of the virus. This might contribute to understanding of why health care workers, who are potentially exposed to larger volumes of viral load, from repeated exposure to infected patients, would have greater risk of severe disease, as has been observed.⁶

In addition to appropriate measures aimed at social isolation, disinfection, and related approaches, this view suggests the importance of support for efficient activation of the innate immune system both pre-infection in susceptible individuals and as an early phase intervention in infected individuals.

However, every immune response against pathogens carries with it, inherently, an incremental increase in inflammatory cytokine activation.⁷ In addition, damage to host tissues drives additional recruitment of neutrophils, macrophages, and other immune elements to the site of

Figure 3. Impact of Timing On Disease Course in COVID-19. Timely type 1 Interferon response yields antiviral response more likely to adequately suppress viral burden, leading to a milder clinical course. Delayed innate immune response, including delayed upregulation of type 1 interferons, may allow greater viral proliferation, leading to more extensive disease and poorer clinical outcomes. Adapted from Channappanavar et al⁵ and Klinker et al.¹¹



infectious damage.⁸ This response can favor pathogen clearance. But, it can also drive more damage, more chemotaxis to recruit immune elements, and creates the potential for an inflammatory loop activation, if signaling chemistry favoring the resolution phase of the inflammatory process fails to turn the tide toward resolution.⁹ This upregulatory loop, involving inflammatory cytokine chemistry and its associated sequelae such as ROS generation and oxidative stress, can drive fatality in COVID-19 disease, characterized by cytokine storm, ARDS, septic shock, organ failure and other factors associated with failure to control proinflammatory activation.¹⁰

It should be noted that field reports raise a question as to whether what's being observed in the lungs of patients with severe forms of COVID-19 should be described as ARDS. Many emergency department and intensive care unit physicians are reporting that the lungs of most of their severely affected patients are not stiff as they would be with ARDS, but virtually all do have extensive microvascular injury on autopsy. These patients also show very high D-dimer levels (personal communication). These observations are consistent with the microvascular thrombotic mechanism described in the NETosis section of this paper. For purposes of this discussion, ARDS will

refer to the COVID-19-specific lung pathology, about which understanding is evolving, recognizing that more clarity regarding the details will emerge with time.

When the time course of a patient's infection with SARS-CoV-2 starts to shift toward upregulation of inflammation and damage to lungs, heart, kidneys, or other organs or tissues, the focus of care may need to shift from an emphasis on support for immune system activation to an emphasis on downregulation of excessive inflammatory response. The challenges associated with inadequate anti-pathogen immune response on the one hand, versus anti-inflammatory immune response on the other hand, has been reviewed.¹¹ Thus, attention must be given to a phased approach to the care and support of patients with SARS-CoV-2 infection, with emphasis on different strategic supports at different phases of the disease process.

The Central Task

Navigating the interplay between early adequate immune activation for antiviral surveillance versus maintaining safe levels of inflammation supporting host survival are key in facilitating a mild disease progression through complete resolution. If the inflammatory process becomes sufficiently

activated, the resulting lung damage can generate more tissue debris that constitutes DAMPs, which will tend to further inflammation.¹² If that reinforcing cycle becomes sufficiently active, the patient can move into cytokine storm, ARDS, septic shock, cardiac or renal damage and other factors associated with fatality risk in COVID-19.¹⁰

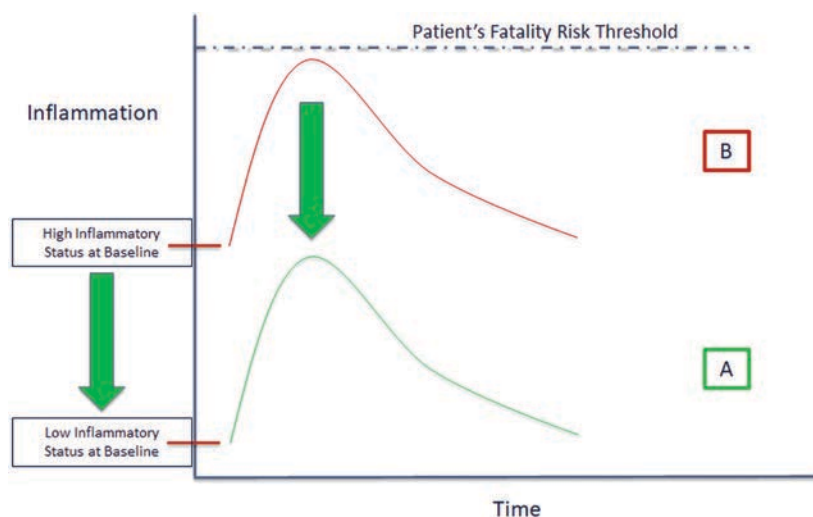
The immune system's process of responding to a pathogen includes effects that are inherently inflammatory. It's important to recognize that "inflammation" is not a single process that simply goes up and down, but an orchestration of interconnected processes with a choreography that normally includes the chemistry of activation—as well as resolution—with many factors involved in regulatory processes that determine to the total outcome. Any and all methods of stimulating, activating and enhancing the immune system's ability to recognize and kill any pathogen, including the SARS-CoV-2 virus, will of necessity involve the immune system generating a cellular and biochemical response, not limited to but including appropriate production of inflammatory cytokines. The immune system is a deeply interconnected system of feedback loops, balances (protease/anti-protease; oxidant/anti-oxidant) and compensatory processes (inflammation/resolution of inflammation). There is no escaping this effect.

Adequate activation > appropriate immune response > > pathogen eradication & triggering of resolution phase chemistry > resolution

Excessive activation > epithelial & endothelial tissue damage > DAMPs/PAMPs > further inflammatory cytokine generation > increased influx of immune elements (neutrophils, macrophages, etc.) > more damage > loop (failure of resolution)

So, any clinical intervention that involves supporting anti-pathogenic immune responses needs to be introduced and sustained with discernment, as excessive inflammatory activation or a skewing toward oxidative stress risks driving the patient to express a potentially excessive inflammatory response. For every patient, there is a moving, multifactorial equation that determines the status of their interconnected systems such as the inflammatory process specifically (itself multifactorial), the effectiveness of resolution chemistry and other modulating mechanisms, and their overall host defense response generally – all against the backdrop of any co-morbidities or pre-existing conditions/disease. This set of variables needs to be addressed with discernment when crafting approaches in the clinical setting. For some patients, concerns about

Figure 4. The patient's baseline level of pulmonary and systemic inflammation may in some cases impact their fatality risk. In **A**, the patient's baseline level of inflammation at onset of infection is modest. As the immune response to the virus evolves, inflammatory cytokines are generated, moving the patient further up the vertical axis. However, the patient's biology can accommodate this increase, as the incremental increase in inflammation is far from that which might risk moving the patient into manifesting ARDS, septic shock, heart or kidney failure, etc. In **B**, the patient's baseline level of inflammation at onset of infection is higher. The same incremental additional inflammation associated with the immune system's choreography of responding to the virus moves the patient correspondingly further up the vertical axis, moving the patient closer to the threshold of manifesting ARDS or other fatality risks. It's noteworthy that, in some cases, inflammation may rapidly escalate from a low baseline to an excessively vigorous inflammatory response that puts the patient in jeopardy, for a host of reasons both known and unknown. So, a low starting inflammatory baseline may not be decisively protective. Nonetheless, moving the patient down the vertical axis, so that the crescendo of the inflammatory process inherent in killing virus doesn't bring them across their threshold of fatality risk, is a worthy clinical goal that may improve the patient's outcome.



specific system processes may be irrelevant. For those for whom SARS-CoV-2 infection may create a substantial morbidity and/or mortality risk due to more aggressive or extensive disease, excessive inflammatory activation is a concern which requires consistent, high level clinical attention. Since there are cases in which young, fit, healthy patients have died of COVID-19,¹³ this discernment must be applied in every case.

Clinical Strategy for Patient Support in COVID-19

This section describes strategy. The section that follows populates the strategy with tactics.

Four Phases in the Time Course of COVID-19

We propose four phases in the time course of the disease, requiring different points of emphasis in the clinical support strategy.

Phase 1 - Prevention

In the Prevention Phase, in addition to guidance about social distancing, masks, stress reduction, etc., the task is to support the patient in anticipation of the possibility that they'll contract the virus. This is accomplished by A) identifying and addressing ways to reduce baseline inflammation, and B) identifying and addressing deficiencies in key nutrients that are central to healthy, robust immune system activation.

Part of the clinical task in this Phase is to triage patients as to risk factors for developing severe course of COVID-19. The main non-pulmonary risk factors identified thus far are hypertension (HTN), diabetes, cardiovascular disease¹⁴⁻¹⁶ and malignancy.¹⁶ Pulmonary risk factors include asthma,¹² COPD,¹⁶ and other respiratory diseases that would suggest the patient would be more likely to enter the Escalating Inflammation Phase if they become infected. Environmental inflammatory stressors like air pollution have been shown to increase lung inflammation affect patients with respiratory disorders.^{17,18} Two cases of early COVID-19 have been described in patients undergoing lobectomy for adenocarcinoma.¹⁹ Liver and kidney injury are also mentioned.¹⁰ Obesity has also been reported as a risk factor²⁰ In the H1N1 epidemic, obesity and severe obesity were significant risk factors.²¹

Furman, et al, found that patients over the age of 85 who had greater expression of specific inflammasome gene modules had markedly greater all-cause mortality. The same paper also showed an inflammasome mediated activation of platelet aggregation that may not be age related.²² That's important, given concerns about thrombotic events in COVID-19. It is useful to notice that biology of inflammasomes, a key intracellular mechanism that drives inflammation, plays a central role in diabetes, CVD, and obesity,²³ in renal disease,²⁴ in liver disease,²⁵ and in pulmonary inflammation.^{12,26}

For higher risk patients, it may be appropriate to consider early initiation of tactics that appear in the Infection Phase. This lets the high-risk patients get a head start on immune activation.

Phase 2 - Infection

In this Phase, the patient has symptoms that may be presumed to be related to the SARS-CoV-2 virus that causes COVID-19 disease. They may have tested positive for the virus. They may have respiratory or GI symptoms, fever, or other onset of new symptoms. The focus in this Phase is on supporting the components of immune system function that are essential to the patient's ability to fight the infection.

Phase 3 - Escalating inflammation

COVID-19 can enter a dangerous phase in which extreme upregulation of inflammatory cytokines can pose mortal danger.²⁷ The clinical goal in this Phase is to help the patient stay away from manifesting the excessive inflammatory cytokine production and tissue destruction associated with sepsis,²⁸ ARDS, and cardiovascular events.^{14,29,30} Natural approaches here are supportive, not primary. The unfolding disease process can escalate rapidly.³¹

The current prevailing hypothesis is that a substantial component of the inflammatory process in COVID-19 is driven by activation of the nucleotide binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome.^{32,33} Inflammasome-mediated lung inflammation has previously been described as steroid-resistant.¹² Current observations from inpatient settings describe steroids as having equivocal evidence in early acute circumstances, and being ineffective in progressed severe forms of COVID-19.³⁴

It's noteworthy that, in addition to asthma²⁶ and COPD,¹⁶ non-respiratory risk factors like cardiovascular disease, obesity, diabetes, and chronic kidney disease, that present greater mortality risk in COVID-19, share the feature of having NLRP3 inflammasome activation as a key component of their etiologies.^{23,35} This connection seems relevant, though whether the greater risk in patients with these diseases is a consequence of greater tendency to vigorous epigenetic expression of NLRP3 or some other mechanism is not clear. Given the speed with which these cases can decline (<24 hrs), it becomes essential to discern the inflection point at which more vigorous measures must be taken to address declining function.

Particular attention may be usefully focused on the relationship between NLRP3, transforming growth factor beta (TGFβ), reactive oxygen species (ROS, and glutathione (GSH). In SARS-CoV-1, the virus upregulated TGFβ via the ROS/p38 MAPK/STAT3 pathway, which correlated with upregulation of profibrotic responses in vitro and in vivo.³⁶ The role of NLRP3 in inducing TGFβ-mediated activation of fibroblasts has been reviewed,³⁷ as has the

role of the NLRP3 inflammasome in organ fibrosis and its follow-on consequences for substantial subsequent mortality risk.³⁷ TGF β is known to drive fibroblast and fibrocyte transformation into myofibroblasts, the cells responsible for the development of tissue fibrosis.³⁸ TGF β and ROS reinforce each other's activation.³⁸ Production of (ROS) can further drive lung fibrosis³⁹ and can also promote further NLRP3 inflammasome upregulation,^{33,40,41} completing a positive feedback loop.

Inflammasome activation is the driver of autoinflammatory disease.⁴² There is a noteworthy association between autoimmune diseases and autoinflammatory disease, with inflammasome activation driving inflammation in many autoimmune diseases.^{43,44} This suggests that patients with autoimmune disease in outpatient clinical settings may need to be followed with heightened discernment regarding their risk of shifting into a course of disease process that enters the Escalating Inflammation Phase.

NETs, Thrombosis, Sepsis, and Fibromyxoid Exudates. Increased risk of thrombosis⁴⁵ and septic shock²⁸ have been described in COVID-19. At autopsy, the alveoli are described as containing cellular fibromyxoid exudates.⁴⁶ In February, a Chinese respiratory expert described COVID-19 as involving a “large amount of very sticky mucus in their small airways.”⁴⁷

Thrombosis, sepsis, and thick mucous secretions share neutrophil extracellular traps as a common causal agent. In addition to phagocytosis and degranulation, neutrophils can kill pathogens by extruding neutrophil extracellular traps (NETs), a process termed NETosis. NETs have been identified in the lungs of cystic fibrosis (CF), acute lung injury (ALI), allergic asthma, and lungs infected with bacteria, virus, or fungi.⁴⁸ NETs have been shown to predict adverse outcomes in community acquired infections such as pneumonia.⁴⁹ A NET is a chromatin mesh, adorned with anti-microbial peptides and enzymes like neutrophil elastase.^{50,51} With increased ROS, a shift toward excessive NETosis drives a significantly exaggerated inflammatory response.⁵² Exaggerated NETosis has been described in diabetes and cardiometabolic disease,⁵³ risk factors that drive greater mortality in COVID-19.

The NETosis response in acute infection can trigger thrombosis. This has been termed immunothrombosis.⁵⁴ NETs have been shown to drive death of epithelial cells and endothelial cells, through a histone-dependent mechanism.⁵⁵ Extracellular histones, the primary protein of the chromatin mesh of NETs, have been shown to contribute to mortality in sepsis.⁵⁶ NETosis contributes to the picture of septic shock.^{48,57}

NETosis is involved at the site of lung infection, where it increases mucous viscosity,⁵⁸ and in the circulation, where it can promote clot formation.^{59,60} NETs appear to provide a third form of clot-forming scaffold, in addition to fibrin and vonWillebrandt Factor (vWF).⁶⁰

Interleukin-6 (IL-6) is a potent inducer of NET formation.⁶¹ This is particularly interesting, in light

of the focus on therapeutic downregulation of IL-6 in COVID-19.⁶² Of note, CXCR2 antagonism, which inhibits neutrophil migration to sites of infection, plays a down-regulatory role in circulating neutrophil NET formation in COPD.⁶³ Therefore, therapeutics that can slow/prevent neutrophil migration⁶⁴ may be of clinical benefit as another mode of dampening inflammation-based processes that contribute to COVID-19 morbidity.

Phase 4 - Recovery

Disease sequelae, including persistent organ dysfunction, are a significant concern, particularly related to acute lung injury⁶⁵ and fibrosis. In SARS-CoV-1, 20% of recovered patients had fibrotic disease nine months post infection.³⁶ Given the apparent role of the NLRP3 inflammasome in COVID-19, and the role of NLRP3 in driving TGF β -mediated fibrosis mentioned already, it becomes essential to attend to the patient's potential need for persistent downregulation of inflammasome biology, with the goal of mitigating risk of additional consequences from non-lethal but nonetheless life changing sequelae related to lingering inflammatory and fibrotic effects that occur in the tail of the curve after the crescendo of disease has passed. As mentioned above, because patients have been observed to relapse into the Escalating Inflammation Phase, it is essential for clinical surveillance to continue well into what may appear to be the Recovery phase.

These Phases and their corresponding clinical imperatives are interconnected and bidirectional. There is both a sequencing as the patient transitions between them and an order of importance of tactics to address each of them, addressed in the tables that describe the tactics. If the patient becomes infected, the very same clinical goals that are appropriate to the Prevention Phase (avoiding infection and early virus clearance) will continue to apply as in the Infection Phase. The key tactical transition occurs if the patient enters the Escalating Inflammation Phase.

Five Targets of Support

There are five types of clinical support that target specific patient immune functions. Some forms of support are appropriate to all Phases in the time course of the disease. Others need to be emphasized or deemphasized, depending upon the Phase. Taken together, the five Targets of Support represent a strategy that can be deployed across the four Phases in the time course of the patient's illness.

Target 1 - Foundational Support

In addition to core approaches involving isolation, disinfection, and other such factors, foundational support involves several key components:

- a. **Eliminating factors that can drive non-purposeful inflammation and related dysregulatory impacts on immune function.** The patient's inflammatory baseline status is influenced by pre-existing

inflammatory conditions. An opportunity presents itself in the non-infected patient (and potentially in the infected patient early in the course of the disease) to reduce non-purposeful contributions to their level of inflammation, to mitigate the risk of the patient entering the Escalating Inflammation Phase, should they become infected. Several potential areas of interest should be included in the clinical inventory:

- i. **Sleep** – Healthy sleep promotes T helper type 1 (Th1) cell response. Th1 cells secrete interferon gamma (IFN γ) that supports anti-viral immune response. Disordered sleep promotes inflammation and Th2 response, at the expense of healthy Th1 response.⁶⁶
- ii. **Stress** – Stress chemistry is inherently inflammatory.^{67,68} The immune suppressive effects of cortisol are well known. The challenges related to using corticosteroids in the COVID-19 context have recently been reviewed.⁶⁹ A recent review examining corticosteroids in COVID-19 suggested possible utility in the early acute phase, but pointed out that conflicting evidence suggests this is not conclusive.³⁴ As mentioned previously, other research has suggested that lung inflammation driven by the NLRP3 inflammasome mechanism is steroid resistant.¹² Interleukin-1 β (IL-1 β) production is driven by NLRP3 inflammasome activation, and drives autocrine loop activation in macrophages and other cells in which NLRP3 activation is taking place, reinforcing Signal 1 of the inflammasome assembly sequence.²³ Non-steroidal treatments targeting inflammasome activation, specifically the IL-1R antagonist anakinra, has been shown to block LPS-induced neutrophil influx in healthy subjects.⁶⁴
Cortisol and norepinephrine elevation have also been shown to induce apoptosis of Th1 cells and NK cells in TBI⁷⁰ and drive Th2 responses in response to inhaler use in asthma.⁷¹ Though the experience of having COVID-19 would itself be considered a source of acute stress, it should be considered that, in many cases, the acute stress is occurring on top of weeks or months of chronic stress associated with social isolation and related factors.
- iii. **Glycemic control** – Insulin resistance, obesity, and impaired glucose tolerance have all been shown to be associated with inflammation.⁷²⁻⁷⁴
- iv. **Dietary factors** – Improvements in diet are strongly associated with reductions in inflammation.⁷⁵⁻⁷⁸
- v. **Microbiome Balance** – Both the lung and the GI tract have a normal microbiome and the complex relationship between the microbiota of the lung and GI tract, and its bidirectional influence with the immune system, has been reviewed.

Dysregulation of the balance of GI microbiome bacteria has been shown to be a source of systemic inflammation.⁸⁰⁻⁸³ Intestinal metabolism of dietary fiber and the resulting increase in short chain fatty acids (SCFAs), specifically propionate, has been shown to enhance hematopoietic generation of macrophages and DC's seeding the lungs. The DC's had increased phagocytic capacity and decreased capacity to induce Th2-bias in lung T cells, an effect that reduced Th2 inflammation.⁸⁴ Exacerbations of chronic lung diseases have been proposed to be episodes of lung microbial dysbiosis.⁸⁵ The status of the lung microbiome may be especially important in situations requiring the use of ventilators, as depletion of the lung microbiota by broad-spectrum antibiotics prior to high tidal volume ventilation was shown to render mice more susceptible to developing ventilator-induced lung injury.⁸⁶

- vi. **Exercise** – Physical activity has long been known to be critical for proper function of virtually all physiological systems. However, to decrease inflammation the right intensity is critical with moderate levels effective at lowering inflammatory markers while intense exercise does not.⁸⁷ IL-6 drives significant inflammatory pathology in COVID-19, as discussed here. Skeletal muscle has been shown to produce and releases significant levels of IL-6 after prolonged exercise,⁸⁸ so caution should be used when considering the form and duration of exercise.

b. Supporting levels of vitamins and minerals with known immunological roles. (see details and references in Tactics section below)

c. Identification of risk factors that represent increased risk of the patient entering the Escalating Inflammation Phase, if they were to become infected with SARS-CoV-2. Patients in this category are likely candidates for NK cell and Th1 cell support at baseline. (see details and references in Tactics section below)

Target 2 - Natural Killer (NK) cell support

NK cells drive the core immunological response to viral infection. The diversity of NK cell types and their roles in the healthy and diseased lung have been reviewed.⁸⁹ Their overall immunological relevance and coordination with Th1 cells in antiviral immune response are discussed in tandem with the Th1 cell discussion below.

Target 3 - T Helper Type 1 (Th1) cell support

Th1 cells play a key role in antiviral immunity. Th1 cells and NK cells support each other's activation via their loop-reinforcing interactions with macrophages.

This effect is mediated by interleukin 12 (IL-12) made by macrophages that activates the NK and Th1 cells, and by IFN γ made by NK cells and Th1 cells that activates the macrophages and stimulates the macrophages to more rapidly and fully destroy pathogens they have phagocytosed. This is central to the adaptive immune response to viral illness. Th1 response also promotes CD8 cytotoxic T lymphocytes (CTLs) which are essential to antiviral immunity.⁹⁰ (CD8 cells are not immune suppressive, despite the lingering terminology).

In a study of COVID-19 patients, the total number of NK cells and CD8 cells has been shown to be markedly decreased, with markers also showing their function to be exhausted. Importantly, NK cell and CD8 cell numbers and function rebound during patient recovery.⁹¹ By contrast, a case report involving a single patient showed significant Th17 cell activation and CD8 cells that were highly cytotoxic and produced copious granzymes and perforin, perhaps associated with the specific treatment strategy employed in the case.⁴⁶ This highlights the necessity of attending to each case through the lens of attention to the individual patient's underlying immunology, with crucial attention to the balance of immune surveillance and activation on one side and the need to downregulate excessive inflammatory activation on the other.

Crucially, the IFN γ generated by both NK cells and Th1 cells drives macrophages to execute a more aggressive program of destruction of the pathogens the macrophages have engulfed by phagocytosis.⁹⁰ Supporting NK cell and Th1 cell activation drives the production of IFN γ , supporting this function.

There is a prevailing concern in the literature about macrophages and DCs being infected and destroyed by the SARS-CoV-2 virus.¹ It is established in immunology that viruses can escape from phagosomes after engulfment by macrophages and DCs. Normally, the macrophage or DC can handle this event through proteasomal degradation and subsequent presentation of the viral antigen via MHC-1 to naïve T cells that become CD8 cytotoxic T lymphocytes (CTLs) that kill the infected cell, so the virus can't use the cell machinery to replicate. However, given the concern about the SARS-CoV-2 virus engaging pathogen evasion strategies that include delaying macrophage responses and potentially destroying macrophages, a key way to push back against this effect would be to shorten the time course between macrophage/DC phagocytosis of a virion (viral protein/viral particle) or virally infected cell and the time point at which the engulfed material is lysosomally degraded. This is a generally recognized function of IFN γ .⁹⁰

Th2 Dominance Patterns Can Thwart the Attempt to Support Th1 Response

In some patients, there may be a cause for concern regarding a prevailing Th2 dominance. Th2 cells make interleukin-4 (IL-4), inhibits the production of Th1 cell

effector cytokines, chiefly IFN γ .⁹²⁻⁹⁴ Factors that diminish the Th1 response raise concerns about blunting overall efficiency of the anti-viral immune response.

It may be crucial in specific patients to downregulate an excessive Th2 dominance, in order to promote an adequate Th1 response. Many factors common in chronic illness can drive the patient into Th2 dominance, including stress chemistry (cortisol and NE),^{70,71} sleep disruption,⁶⁶ asthma,^{95,96} and GI tract inflammation,^{96,97} among others. Asthma patients are known to be predominantly Th2 dominant, as are patients with allergic or atopic immune styles.⁹³

Diminished reduced glutathione (GSH) status is also associated with loss of IFN γ , increase in IL-4, and a shift away from adequate Th1 response and into Th2 dominance.⁹⁸⁻¹⁰⁰ This is especially concerning in light of the mutually reinforcing roles of ROS and TGF β in inflammation and fibrosis discussed earlier. Depletion of GSH in lung epithelial lining fluid (ELF) carries concerns about loss of anti-inflammatory protection in lung¹⁰¹ as well as a shift away from anti-viral Th1 response referenced above.

Additional concern regarding excessive Th2 response to the detriment of adequate Th1 comes from evidence that coronaviruses, in this case coronavirus NSP6 protein, interferes with proper formation of autophagosomes in such a way as to prevent merging with lysosomes. The result may be interference with the ability of immune cells to kill virus.¹⁰² It's noteworthy that IFN γ (the primary Th1 cytokine) is required for autophagosome formation and that IL-4 (the primary Th2 cytokine) interferes with this process.¹⁰³⁻¹⁰⁵ The machinery of autophagy is known generally to be required for macrophage phagocytosis and autodigestion of phagosome contents. Thus, the emphasis on Th1 may have an added utility if SARS-CoV-2 also targets interference with autophagy as a component of its pathogen evasion strategy.

Lastly, animal coronavirus models¹⁰⁶ have shown that mast cells residing in the respiratory submucosa may play a mixed role, including the generation of Th2 pro-inflammatory cytokines under the influence of viral stimulation and IgE, an antibody type associated with Th2 style immune reaction. Mast cells are stimulated by interleukin-5 (IL-5), a cytokine secreted by Th2 cells. Quercetin has been shown in many human studies to modulate mast cell degranulation.¹⁰⁷

Target 4 – Anti-Inflammatory Support

The key targets in inhibiting inflammation are the NLRP3 inflammasome, and Nuclear factor kappa B (NFkB).

NLRP3. This is the inflammasome currently hypothesized to drive lung inflammation and some ARDS fatality risk in COVID-19.³² The role of the NLRP3 inflammasome in sepsis has been reviewed.¹⁰⁸ Inflammasome assembly causes the affected cell to

release IL-1 β and IL-18 into the tissue environment,¹⁰⁹ and occurs in response to a wide range of factors, including K⁺ and/or Cl⁻ efflux from cells, low systemic pH, high glucose, ROS, cholesterol, uric acid, and other factors.⁴⁰

There are two signals that drive classical inflammasome assembly:

Signal-1 - cell membrane receptor stimulation by IL-1 β .

This induces an increase in cytosolic NF κ B, which in turn induces gene expression of pro-IL-1 β and pro-IL-18.

Signal-2 - (activation triggered by PAMPS & DAMPS) involves P2X7 receptor stimulation by extracellular ATP from adjacent or nearby cells that are dying, releasing their cytosolic ATP into the extracellular space. It is noteworthy that Ion flux is an important driver of NLRP3 activation, specifically K⁺ and Cl⁻ efflux out of the cell and elevated intracellular Ca²⁺, so anything that inhibits K⁺ and Cl⁻ efflux and lowers cytosolic Ca²⁺ will contribute to inhibition of NLRP3. Downstream of ion changes is ROS production from stimulated mitochondria that leads to NLRP3 formation, suggesting the utility of anti-oxidants.

There is also a newer alternate/non-classical inflammasome activation of NLRP3 in monocytes (not macrophages) that is K⁺ independent and requires toll-like receptor 4 (TLR4) ligands, i.e., lipopolysaccharide (LPS), a gram negative bacterial PAMP.¹¹⁰ This pathway's activation suggests that measures taken to lower baseline LPS levels would have merit. Increased absorption of LPS is found in intestinal dysbiosis, which is associated with chronic upregulation of systemic inflammation that is reversed by restoration of appropriate gut microbial balance.¹¹¹

Given that Signal-2 is stimulation of P2X7 receptors by ATP spilled from the cytosol dying adjacent cells, it may be important to consider avoiding supplements purported to contain ATP or promote ion imbalance per above. Those containing adenosine may also be inappropriate, as adenosine induces T effector cell anergy.¹¹²

NF κ B. NF κ B is the key pro-inflammatory protein complex at the center of the NF κ B / IL-1 β and TNF α activating loop that drives pro-inflammatory cytokine production at the center of the immune response to pathogens and damage.⁸ NF κ B is produced in response to Signal-1 (priming) of the NLRP3 inflammasome assembly cycle that produces IL-1 β and IL-18 and drives pyroptosis (a highly inflammatory form of programmed cell death). Inhibiting NF κ B activation or stimulating I κ B (inhibitor of KappaB) is therefore anti-inflammatory. In SARS-CoV-1, spike protein activation of IL-6 and TNF α were shown to occur through upregulation of NF κ B.¹¹³

Target 5 – Anti-Oxidant Support

GSH and N-acetylcysteine (NAC) play particularly important roles in anti-oxidant support in COVID-19. GSH and NAC are both components of normal human biology. GSH appear to play a key role in supporting both the immune surveillance and anti-oxidant/anti-inflammatory components of the strategy for addressing care for patients with COVID-19. The biological role of GSH in respiratory illnesses including ARDS has been reviewed.¹¹⁴ The role of GSH in promoting NK cells and inhibiting macrophage infection in TB has been reviewed.¹¹⁵

GSH plays a key role in the lung, with the level of GSH in the lung epithelial lining fluid (ELF) strongly influencing the extent of lung inflammation and maintaining oxidant/anti-oxidant homeostasis.¹⁰¹

GSH, in addition to its known anti-oxidant function and anti-inflammatory role, is essential for other functions of the immune system, both innate and adaptive: these include T-lymphocyte proliferation^{116,117} phagocytic activity of polymorphonuclear neutrophils (PMN)¹¹⁸ and dendritic cell functions¹¹⁹ that are crucial to adaptive immune system activation, as DCs function as the professional antigen presenting cell (APC).

N-Acetyl Cysteine. Oral NAC is readily absorbed through the stomach and gut and is converted to cysteine in the liver via first pass metabolism. The majority of cysteine is secondarily incorporated into GSH and released into systemic circulation.¹²⁰ Availability of cysteine is the rate limiting factor in GSH synthesis.

The potentially crucial role of neutrophil extracellular traps (NETs) has been discussed above, including promotion of thrombus formation, increased mucous viscosity, epithelial and endothelial cell destruction, and sepsis, and the role of IL-6 as a driver of NETosis. NAC downregulates NET formation through the downregulation of ROS.⁵⁸ NAC has been shown to exert an anti-thrombotic effects,¹²¹⁻¹²³ and increase intraplatelet GSH and reduce platelet ROS.¹²¹ NAC is an accepted treatment for patients with cystic fibrosis. In addition to its directly mucolytic properties, the influence of NAC in reducing ROS and down-regulating NETosis might also be expected to favorably influence these other observed NET-mediated destructive effects in COVID-19 patients.

Inhaled NAC is a well-recognized mucolytic agent and has been a mainstay intervention in cystic fibrosis (CF) patients since the 1960's. In addition to its mucolytic properties, NAC is anti-inflammatory and antioxidant. In one pediatric trial (N = 120 in NAC group), inhaled NAC was well tolerated long-term and attenuated rate of decline in FEV1, outperforming other commonly used mucolytic agents hypertonic saline and inhaled dornase-alfa.¹²⁴

In healthy adults with poor mucociliary escalator function, a 600 mg dose of oral NAC improved mucociliary escalator function by 35%, with washout yielding return to baseline.¹²⁵

Figure 5. The relationships between TGF β , GSH, ROS, fibrosis, alveolar inflammation, and NETosis in processes occurring at sites of local infection/inflammation. As with all such maps, the reality of the underlying biology is more deeply interconnected.

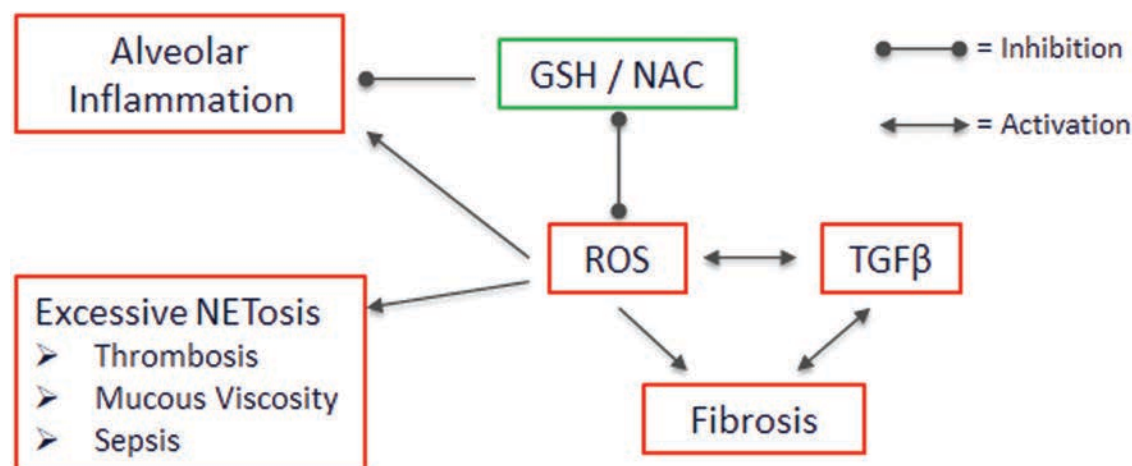
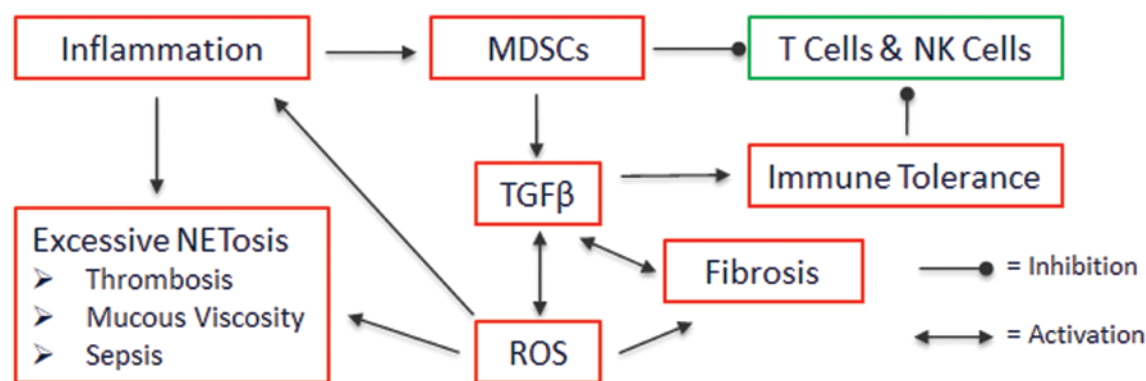


Figure 6. The impact of MDSC / TGF β / ROS interactions on T Cells and NK Cells.



Glutathione-TGF β Relationship. The reciprocally inhibitory roles of TGF β and GSH have been described.³³ GSH plays key roles in the context of respiratory anti-inflammatory support and mitigating the risk of fibrotic damage to lungs and other organs:

- Taken up directly by macrophages through micropinocytosis (anti-inflammatory)¹⁰¹
- Necessary for Th1 response⁹⁸⁻¹⁰⁰
- Key inhibitor of TGF β :¹²⁶
 - TGF β has been studied in SARS-CoV-1, in relation to lung fibrosis.³⁶
 - TGF β inhibits GSH formation enzymatically, so these are in reciprocal inhibition.¹²⁷
 - TGF β drives generation of ROS that damage the lung both directly and by inducing NLRP3 inflammasome formation, referenced above.
 - TGF β promotes fibrosis, referenced above.

The role of ROS in upregulating the NETosis that drives sepsis, destruction of epithelial and endothelial

tissue, thickening of mucous secretions, and thrombus formation has already been discussed. Figure 5 describes the relationships between various factors in this process.

MDSCs. In chronic inflammatory states, in the tumor microenvironment, and in infection, immature myeloid cells can be diverted into becoming myeloid derived suppressor cells (MDSC's), instead of maturing to their normal fates as neutrophils, macrophages, and DCs. These MDSCs pour out excessive amounts of TGF β , driving depletion of GSH and generation of additional ROS. This can become another factor in the further upregulation of inflammation and fibrosis.¹²⁸ Added ROS will also drive further expression of NETosis.

Both GSH and NAC have been shown to stimulate effector T cell proliferation.¹²⁹ MDSCs take up cysteine as a means of depriving effector T cells of the capacity to activate.¹²⁸ Given the preliminary evidence that extent of lymphopenia is related to lethality of COVID-19,² adequacy of cysteine in tissues may be an important protective factor.

Tactics to Support the Clinical Strategy

Assessment of Risk Factors

Identifying whether the patient is at increased risk of severe disease course and poorer outcomes with SARS-CoV-2 infection is critical. As an early robust immune response may be predictive of a milder form of disease,⁵ patients at greater risk may be candidates for NK cell and Th1 cell support at baseline, rather than waiting until they become infected.

The mechanisms underlying various risk etiologies may give perspective to the individual case and provide clues as to how to treat the patient, with the goal of minimizing these risks.

Health Care Workers

Health care workers, who are potentially exposed to larger volumes of viral load, from repeated exposure to infected patients, have been observed to be at greater risk of developing more severe forms of COVID-19.⁶

Older Individuals

Hospitalization rates for COVID-19 increase with age and are highest among older adults; the majority of hospitalized patients have underlying conditions.¹³⁰ Immune function declines with age, particularly T cell-mediated activity, which increases morbidity and mortality from infectious disease. Thymus involution is correlated with aging and loss of T cell activity. Select nutrients recommended in the five Targets of Support and elsewhere including zinc and vitamins A and D have recognized benefit on thymus function and T cell status, and may therefore be especially beneficial for older individuals.^{131,132}

Older age carries with it the likelihood of onset of Immunosenescence.¹³³ Immunosenescence may increase the risk of contracting an infection and may also make it harder to clear infections. In older humans, macrophages become less efficient, phagocytize less, and secrete more inflammatory cytokines. This age-associated low-level inflammatory upregulation is termed “inflammaging.” Inflammaging may contribute to poorer immunological outcomes, manifesting as both less efficient macrophage pathogen clearance and greater macrophage production of inflammatory cytokines.¹³⁴ Inflammaging is consistent with the description of macrophage activation syndrome (MAS), described as contributing to increased COVID-19 age-related mortality.¹³⁵ In MAS, macrophages produce excessive amounts of inflammatory cytokines. This is consistent with the inflammaging model. Inefficient macrophage mediated pathogen clearance would perhaps explain the observation that, early in the disease process, the innate immune system fails to adequately suppress proliferation of the virus, and yet there is copious infiltration of innate immune cells in the lungs of patients with progressed disease. In an autopsy study of six SARS-CoV-1 patients, four were found to have giant cell

infiltrates, with increased macrophages in the alveoli and interstitium.¹³⁶ Inflammatory cytokine production by macrophages would also induce vigorous neutrophil chemotaxis to sites of inflammation, driving the NETosis referred to elsewhere in this paper. There is significant ongoing discussion of senolytics for the treatment or prevention of COVID-19.¹³⁷

Patients With Known Comorbidities

The risk factors discussed earlier need to be identified, particularly including hypertension, diabetes, cardiovascular disease, malignancy, respiratory problems, and obesity. Underlying upregulation of NLRP3 expression in these diseases suggests that inhibition of the inflammasome, perhaps through greater emphasis on tactics in the Foundational and Anti-inflammatory Targets of Support categories, starting at baseline, may be essential in patients with these risk factors.

Patients With Respiratory Problems

Fibrotic diseases like idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, and COPD may confer significantly increased risk. An established fibrotic mechanism involving TGF β suggests that, in addition to NLRP3 inflammasome inhibition, greater emphasis may need to be placed on GSH¹²⁶ and vitamin D,¹³⁸ as both can inhibit TGF β . This may be appropriate early in the clinical course of these cases, and/or as part of an overall prevention strategy in cases with these features.

Patients With Genetic Susceptibilities. As part of the assessment of patient risk factors, genotype testing to assess patient GSH functional capacities may be clinically useful. For example, patients with exaggerated inflammatory neutrophil response to inhaled ozone were 13x more likely to carry the GSTM1null genotype.¹³⁹ If infected, these patients might more readily enter the Escalating Inflammation Phase of COVID-19. Higher doses of GSH and NAC may be appropriate in these cases, to compensate for the genotypic disadvantage.

See also the discussion of polymorphisms related to zinc and IL-6 in the discussion of zinc.

Tactics for the Five Targets of Support

This section describes the tactics associated with each of the five Targets of Support. It's important to understand which tactics to apply throughout, and which ones to emphasize during specific Phases of the disease process. Information in the tables and text, along with the clinician's unfolding work with the patient, form the basis for that discernment.

1. Foundational Support

To address foundational support, clinicians can consider addressing factors that impact immunological integrity as well as factors that drive non-purposeful inflammation.

Address factors known to impact immunological integrity

a. Sleep - Healthy sleep is anti-inflammatory and promotes appropriate Th1 response. Disordered sleep is characterized by reduced sleep efficiency, less slow wave sleep, and more REM sleep. Disordered sleep yields increased inflammation and increases Th2 response at the expense of Th1 response.⁶⁶

Sound sleep hygiene practices, reviewed elsewhere,¹⁴⁰⁻¹⁴³ are fundamental for promoting healthy sleep. In addition, substances such as melatonin may be added to enhance sleep promotion. Not only is melatonin a useful sleep aid, it also inhibits NLRP3 inflammasome activation,¹⁴⁴⁻¹⁴⁶ and reduces airway inflammation.¹⁴⁷ Melatonin has also been identified as a potential therapeutic drug in an in silico model of the human interactome with SARS-CoV-2 (4).

b. Stress - As referenced earlier, stress chemistry is inflammatory and has been shown to shift the patient away from effective Th1 response. Many patients will have been enduring significant chronic stress by the time they become infected. Though it is not part of the main protocol, for patients with significantly elevated stress levels, it may be useful to give adaptogens like ginseng or ashwagandha.¹⁴⁸⁻¹⁵²

Stress chemistry can and should also be addressed by a number of other techniques that have proven useful for decreasing the stress response. Patient ability and personal preferences will guide the appropriate choices. Techniques include mindfulness-based stress reduction (MBSR)^{153,154} exercise,¹⁵⁵ relaxing music, creative pursuits, biofeedback,¹⁵⁶ and many others, reviewed elsewhere.¹⁵⁷

Eliminating non-purposeful inflammation

Factors known to drive inflammatory activation, such as dysglycemia, dysbiosis, and/or consumption of inflammatory foods need to be addressed.

Glycemic control, dietary factors, and Lung and GI microbiome balance are all essential components of health and essential areas of focus in the functional approach to patient care. In the Prevention Phase, addressing these systems may present a valuable opportunity to reduce the patient's baseline inflammatory status (Figure 4). In the COVID-19 setting, it's essential to consider whether attention to these factors is a suitable area of focus, with considerations including illness phase, patient capacities to follow multiple instructions, and potential for an intervention to affect short term positive impact on patient outcome.

c. Glycemic Control - Addressing glycemic control is a critical part of controlling baseline inflammation. As stated earlier, insulin resistance, and impaired glucose tolerance are associated with inflammation, and may be a contributing factor that puts diabetics at a higher

risk for severe COVID-19 outcomes.¹⁵⁸ Most of the work of achieving optimal glycemic control involves subtracting foods from the diet that contribute to an increased post-prandial glycemic response.¹⁵⁹ This avoids adding to the burden of polypharmacy involved in implementing other tactics. While there is individual variation in what food cause a higher glycemic response in specific individuals,¹⁶⁰ the general advice of reducing foods with a high glycemic load is a good place to start.¹⁶¹ Food combining in order to reduce glycemic burden should also be considered.^{162,163} By monitoring blood sugars using a continuous glucose monitor or intermittent glucometers one can get a good sense of what types of foods increase postprandial glycemic response.¹⁶⁴

d. Other Dietary Factors - Dietary factors in addition to those contributing to disrupted glycemic control should also be addressed. A high quality nutrient dense diet that focuses on eating whole plant-based foods that are rich in healthy fats and phytonutrients (multicolored fruits and vegetables) is foundational to decreasing overall inflammation.¹⁶⁵ Reducing or eliminating inflammation promoting foods is also important. Foods that are highly processed and/or contain chemical additives, trans-fats, oxidized fats and added sugars are inherently inflammatory.¹⁶⁶⁻¹⁶⁸

e. Lung and GI Microbiome - The lung microbiome is closely linked to chronic lung diseases and lung inflammation in a bidirectional manner.^{169,170} Disruption of gut microbiome can increase sensitivity to viral infections,¹⁷¹ while treatment with beneficial probiotics can enhance resistance to viral infection.¹⁷² The role of the gut microbiome in overall inflammation has been well established.^{173,174} In addition, the lung and gut microbiomes both have an intimate relationship to their respective mucosal membranes, which are critical players in early immune protection.¹⁷⁵ Therefore, maintaining a healthy lung and gut microbiome, and maintaining the integrity of the mucosal linings of both systems is important in decreasing overall inflammatory burden. The use of a high fiber, polyphenol rich diet, prebiotics, and probiotics can be considered to promote a healthy microbial ecosystem.¹⁷⁶⁻¹⁷⁹ Avoiding smoking and air pollution also makes sense.^{180,181}

Many of the vitamins, minerals, and botanicals recommended in this paper for their immunological roles also have roles in supporting the microbiome and mucosal membrane integrity and immunity. Vitamin D plays an important role in mucosal immune function¹⁸² and vitamin A is critical in maintaining epithelial barrier integrity.¹⁸³ N-Acetyl Cysteine protects intestinal health via a number of different mechanisms including tight junction signaling.¹⁸⁴

Supporting levels of vitamins, minerals, and other substances with known immunological roles.

The role of nutritional agents as immune modulators has recently been reviewed.¹⁸⁵ It's noteworthy that many of these nutrients play dual roles in immunology, supporting immune surveillance while also reducing inflammation.

Vitamin D - The potential utility of vitamin D in COVID-19 has been reviewed, with the authors recommending a multi-day loading of 10 000 iu qd and a steady dose of 5000 iu qd, with the goal of bringing lab ranges above 40-60 ng/ml.¹⁸⁶

Many studies have shown that vitamin D deficiency not only impairs immune function but also promotes excessive inflammatory reactions. The role of vitamin D in inflammatory and autoimmune disorders has been extensively reviewed, including here.¹⁸⁷ Deficiency has been shown in many inflammatory and autoimmune diseases such as asthma,¹⁸⁸ various types of arthritis,¹⁸⁹ SLE,¹⁹⁰ Type 1 diabetes,¹⁹¹ Multiple Sclerosis,¹⁹² among others. Supplementation is most likely primarily effective in those deficient in vitamin D or with a VDR polymorphism impairing vitamin D absorption and metabolism.¹⁹³

A meta-analysis of studies on vitamin D and acute lung injury (ALI) found that, in studies that did not use very large, rare bolus dosing, vitamin D was safe and protected against ALI. Patients who were deficient and received non-bolus dosing had the most benefit.¹⁹⁴ Vitamin D has been shown to prevent experimental lung fibrosis and predict survival in patients with idiopathic pulmonary fibrosis, via inhibition of TGF β .¹³⁸ TGF β is a central player in lung fibrosis and a central generator of the NETosis discussed above, that is associated with sepsis, thickening mucous secretions, and thrombus formation. Vitamin D has also been shown to reduce the risk of acute respiratory infection.¹⁹⁵

Vitamin D is necessary for the formation of macrophage lysosomal enzymes, a key component of the ability of macrophages to kill pathogens, including viruses, that have been engulfed by phagocytosis.¹⁹⁶ In many experimental models, macrophages are infected with pathogen in vitro, and the cytokine profiles the macrophages generate are measured. As described in the work of Hewison,¹⁹⁶ healthy macrophages with adequate vitamin D status will respond more effectively to infection. This includes greater production of cytokines whose function is to stimulate chemotaxis of neutrophils and other immune elements to the site of infection. Effective neutrophil chemotaxis is induced by inflammatory cytokines, and neutrophil influx into tissue is at the center of normal anti-pathogenic inflammation. These chemical signals are normal in the context of a well-orchestrated inflammatory response, including

the resolution phase. Isolating the role of vitamin D in allowing macrophages to respond normally to pathogens does not reflect the total picture of vitamin D's role in the body. Vitamin D plays a key role in both immune system antipathogenic function and anti-inflammatory functions.

ii. **Vitamin A** - Vitamin A was the first fat-soluble vitamin to be identified. Early researchers found that young animals fed a diet deficient in natural fats became very unhealthy and that their eyes became severely inflamed and infected. Vitamin A was once known as the "anti-infective vitamin," and vitamin A status is a major determinant of overall immune status. Those deficient in vitamin A experience impaired antibody response, decreased levels of helper T cells, and impaired integrity of the mucosal linings of the respiratory and gastrointestinal tracts. Vitamin A-deficient individuals are more susceptible to infectious diseases, respiratory conditions like asthma and allergies, and have higher mortality rates.¹⁹⁷

The prevalence of deficiency is difficult to determine as numbers vary widely worldwide and criteria are inconsistent. Nonetheless, deficiency is common worldwide, with epidemic prevalence in Saharan Arica (48%) and South Asia (44%).¹⁹⁸

Unfortunately, vitamin A deficiency is also common in the US with 34% of adults consuming less than the EAR.¹⁹⁹ Co-author Pizzorno in an unpublished study of retinol levels in 200 adult oil field workers in Canada found that 40% were deficient.

While beta-carotene is commonly considered synonymous with vitamin A, this an error with significant clinical consequences, especially for vegans. Emerging research has shown multiple, surprisingly common, genomic variations that impair conversion of beta-carotene to vitamin A by 24 to 57%. Single nucleotide polymorphisms have been identified that decrease activity of 15,15'-monooxygenase, the key enzyme converting beta-carotene to retinol. rs12934922) and rs7501331 variants have been found in 42% and 24%, respectively. Those with one copy of the less common allele have shown a 32% drop in activity, while those who are homozygous for the polymorphism experience a 57% reduction in conversion rate.²⁰⁰

A controlled animal study in calves found that low dietary vitamin A impaired IgG1 titers against intramuscularly inoculated inactivated bovine coronavirus vaccine.²⁰¹

Vitamin A levels drop during various types of infection and multiple studies have shown that vitamin A supplementation improves resistance and recovery rate.²⁰² Given the numbers above regarding the high prevalence of vitamin A deficiency, this is cause for concern in the current crisis.

Vitamin A, especially when in balance with vitamin D, has low toxicity except at high dosages. For adults, toxicity is typically seen after 100 000 IU/d for 6 months.²⁰³ A study that looked at the positive effects of multivitamin supplementation in women with HIV showed that Vitamin A was detrimental to outcome.²⁰⁴ However, in this study, vitamin A was supplemented in the absence of the other fat soluble vitamins notably D and K. Animal studies have demonstrated that vitamin A both decreases the toxicity of and increases the dietary need for vitamin D and vice versa.²⁰⁵ In addition, concomitant supplementation with vitamin D significantly increased the dose of vitamin A that causes toxicity.²⁰⁶

Multiple studies have shown that vitamin A deficiency increases inflammation and more limited research has shown supplementation decreases inflammation. This appears particularly important for the mucosal barriers. However, the research is complex as inflammation itself appears to decrease blood levels of vitamin A.²⁰⁷

- iii. **Zinc** - Zinc plays a crucial role in the function of essentially all immune cells. Deficiency of this critical element has a profound impact on immune response, increasing susceptibility to a variety of infections.²⁰⁸⁻²¹² One of zinc's critical roles in immune function is its role in thymulin production and activity.²¹³

In addition, zinc has specific and well-known antiviral properties.²¹⁴ Increasing intracellular zinc concentrations in cell culture impairs the replication of a variety of RNA viruses including SARS-CoV-1. Intracellular zinc has been shown to inhibit RNA synthesis by suppressing the SARS-CoV-1 replication and transcription complex.²¹⁵ In vivo evidence for zinc's antiviral role comes from a Cochrane review that found zinc intake was associated with a significant reduction in the duration of the common cold. Many of the studies showing benefit when taken during the course of an infection were in the form of a zinc lozenge.²¹⁶ It makes sense to utilize this mode of delivery during the acute infection phase.

Zinc has also been shown to suppress Th17 cell development.²¹⁷ Interleukin-17 (IL-17) made by Th17 cells has been shown to drive an inflammatory feedback loop via IL-6 induction.²¹⁸ Zinc dependent transcription factors are involved in the regulation of the gene expression of IL-6 and TNF α .²¹⁹ The effect of SNPs in genes encoding zinc transporters on blood zinc levels in humans has been examined.²²⁰ Older individuals with gain of function IL-6 SNPs have been shown to have a greater need for zinc.²²¹ Zinc supplement in older individuals with gain of function IL-6 SNPs and low zinc were shown to have lower IL-6 and MCP-1 levels upon zinc supplementation.²²²

Anosmia (loss of smell) and dysgeusia (distorted sense of taste) are commonly being reported in patients at every phase of COVID-19.²²³ These are also classic symptoms of zinc deficiency. It is too early in the discovery process to determine if this is cause or effect, nonetheless zinc deficiency greatly impairs immune function, especially resistance to viral infections. Notably, inadequate dietary consumption of zinc is found in almost half the older population.²²⁴

- iv. **Vitamin C** - Vitamin C is recognized as an essential nutrient in many aspects of the immune system, especially immune cell function of both the innate and adaptive immune responses.^{225,226} Microbial killing requires vitamin C for chemotaxis, phagocytosis and generation of ROS.^{227,228} Vitamin C deficiency contributes to decreased immune responsiveness and increased susceptibility to infections. Once infected, the enhanced inflammation and metabolic requirements place a further demand for additional vitamin C.²²⁹ Vitamin C supplementation has been shown to both prevent and treat respiratory and systemic infections. The utility of vitamin C and thiamine in sepsis has been reviewed.²³⁰

Optimal cell and tissue levels of vitamin C in the plasma saturation range are needed for prophylaxis, while treatment of infections requires significantly higher doses.^{231,232} In addition, vitamin C's role as an antioxidant is important in protecting the body against the damage from oxidative stress generated during an infection.^{233,234} Vitamin C also plays an critical role in endothelial stability, supporting nitric oxide generation and vasodilation. In light of the coagulopathy found in many COVID-19 patients, this role seems highly relevant.²³⁵

The CITRIS-ALI study, an RCT published in JAMA in 2019, showed a possible decrease in mortality in 167 patients with sepsis-related ARDS receiving ~15 grams/day of IV vitamin C for four days.²³⁶ Recruitment is underway at this writing for an RTC IV vitamin C trial (24g/day) in COVID-19 patients hospitalized with severe pneumonia.²³⁷ At Northwell Hospital in New York, there are multiple anecdotal reports of the use of IV vitamin C (1500 mg TID to QID) in COVID-19 patients. Those receiving the IV vitamin C appear to be doing significantly better than those not receiving it.²³⁸

A meta-analysis of six controlled trials published in March 2019 demonstrated that an average oral delivery of 2 grams of vitamin C per day shortened length of ICU stay by 8.9%. In three trials in which patients required mechanical ventilation for over 24 hours, vitamin C shortened the duration by 18.2%.²³⁹

- v. **Quercetin** - As discussed above, the antiviral roles of zinc are well documented. However, protection of cells against viral appropriation of cellular metabolism to replicate viral RNA requires adequate intracellular zinc. Ionophores play a critical role in facilitating transport of zinc into cells. The commonly available flavonoid quercetin is a zinc ionophore and has been shown to facilitate transport of zinc across lipid membranes. This is particularly relevant as chloroquine is also a zinc ionophore, which has been postulated as a possible mechanism for its apparent efficacy against SARS-CoV-2.^{240,241}

Quercetin is also important as one of multiple flavonoids shown in vitro to block the activity of MERS-CoV 3CLpro, a critical enzyme for coronavirus replication. Animal studies are limited at this time but support efficacy.²⁴²

In a molecular docking study looking for agents that could bind to the SARS-CoV-2 Viral Spike Protein and thus have potential to inhibit its infectivity, researchers found quercetin to be the fifth most effective.²⁴³ However, quercetin has low bioavailability and therefore requires special formulations to achieve clinically effective blood levels. A trial with a phytosomal quercetin formulation has been started in Italy on 660 hospitalized COVID-19 patients (private communication with study PI).

- vi. **Fish Oil** - The role of fish oil in reducing inflammation is long established. However, in an acute care setting, the time scale involved in addressing acute inflammation may preclude the use of fish oil as a strategy for influencing the body's inflammatory equilibrium. Nonetheless, it is worth mentioning the potential role that specialized pro-resolving lipid mediators (SPMs) may play in influencing the biology of risk, in those for whom care is occurring in the Prevention Phase.

SPMs are downstream products of the metabolism of EPA and DHA, the primary active constituents of fish oil. EPA is the precursor for the E series resolvins, and DHA is the precursor for the D series resolvins, neuroprotectins, and maresins.^{244,245} These lipid mediators play a key role in the resolution phase of the inflammatory process.⁹

SPMs can inhibit priming and activation of macrophage NLRP3 inflammasome (in vivo and in vitro). SPMs, specifically D2,²⁴⁶ suppressed IL-1 β production and secretion in LPS- and ATP-challenged macrophages, and reduced inflammasome assembly and caspase-1 activity. D2 also deactivated the inflammasome in a mouse peritonitis model, as shown by reduced IL-1 β release and increased M2 markers of inflammation resolution.

2. Natural Killer (NK) cell support

a. **Radix astragali (Astragalus)** - One of the top prescribed botanicals in TCM preparations for SARS-CoV-1 was Radix astragali, with numerous published clinical trials demonstrating significant efficacy for both prevention and treatment. In SARS-CoV-2, astragalus continues to be the most common botanical in TCM prevention formulas prescribed in China.²⁴⁷

b. **Andrographis paniculata (Andrographis)** - The antiviral properties of andrographis have been proposed as leads for pharmaceuticals in the antiviral drug discovery literature.²⁴⁸⁻²⁵¹ Andrographis has been shown in human randomized controlled trials to be effective in upper respiratory tract infection^{252,253} and pharyngotonsillitis.²⁵⁴ Andrographis has been shown to promote natural killer cell activity^{255,256} and also reduce the levels of inflammatory cytokines.²⁵⁷

c. **Ganoderma lucidum (Reishi mushroom)** - Ganoderma has been used in traditional Chinese medicine (TCM) for thousands of years. The antiviral properties of ganoderma have been studied in dengue,^{258,259} HIV,²⁶⁰ HPV,²⁶¹ enterovirus^{71,262} and herpes.²⁶³ Reishi activates NK cells²⁶⁴⁻²⁶⁸ and Th1 cells^{269,270} and downregulates inflammatory cytokines in human alveolar epithelial cells.^{271,272}

3. Th1 cell support

a. Berberine-containing Botanical Medicines (*Hyrastis canadensis*, *Coptidis Chinensis*)

Berberine has been shown to have activity across a broad range of viruses.²⁷³⁻²⁸⁰ Berberine has activity against RSV via upregulation of type 1 interferons.²⁸¹ Type 1 interferons are key activators of NK cells and play a central role in antiviral immunity.^{282,283} The anti-inflammatory,²⁸⁴⁻²⁸⁶ cardioprotective,^{285,287} and antifungal effects of berberine have also been reviewed.²⁸⁸ One mechanism by which berberine downregulates inflammation is through activation of AMP kinase (AMPK).²⁸⁹ AMPK is a known activator of SIRT2,²⁹⁰ a known inhibitor of NLRP3 inflammasome assembly.²³ Other mechanisms of berberine inhibition of NLRP3 have also been described.²⁹¹⁻²⁹³ Berberine-induced AMPK inhibits IL-6-induced inflammation in human liver cells by inhibiting STAT3, the signal transduction factor required for Th17 cell differentiation.²⁹⁴ Berberine promotes the Th1 cytokines IL-12 and IFN γ and inhibits the Th2 cytokine IL-4.²⁹⁵⁻²⁹⁷

Berberine also has potential advantages in impacting clotting. Hypoxia inducible factor 1 alpha (HIF1 α) has been described as a promoter of thrombosis.²⁹⁸⁻³⁰⁰ As the name implies, HIF1 α is upregulated by tissue hypoxia. With poor oxygenation, higher HIF1 α levels will drive more thrombus formation. As described before, neutrophil NETs offer an additional base material for clot formation.⁶⁰

The combination of these factors may be a driving force in the extensive pulmonary microvascular damage seen in severe manifestations of COVID-19. Berberine has been shown to downregulate HIF1 α .³⁰¹⁻³⁰⁵

In a human trial with 130 acute coronary syndrome subjects receiving percutaneous coronary intervention, those receiving 300 mg of berberine TID for 30 days had significant reductions in matrix metalloproteinase (MMP)-9, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, C-reactive protein, IL-6 and monocyte chemoattractant protein-1 (MCP-1), all of which are inflammatory signaling molecules.³⁰⁶

Goldenseal is often used because its high concentration of berberine. In a study examining the inhibition of influenza A by berberine, goldenseal at higher dosages was found to be effective at inhibiting both growth of influenza A and production of TNF α and PGE2.³⁰⁷

b. Baicalin-containing Botanical Medicines (*Scutellariae baicalensis* (SB) and other *Scutellaria* spp.) - The high infectivity rate of SARS-CoV-2 separates it from the genetically similar SARS-CoV-1. Preprint research suggests that one difference might lie in a unique furin-like cleavage site on the SARS-CoV-2 Spike protein that is absent in SARS-CoV-1.³⁰⁸ Dengue virus also infects human cells via furin cleavage, and could be inhibited in vitro and in vivo by application of the flavonoid luteolin.³⁰⁹

Evidence for antiviral, antioxidant, and anti-inflammatory effects of SB has been reviewed.^{310,311} The ability of SB to downregulate Th17 cell differentiation, the major source of IL-17 that induces macrophage IL-6 production, has been reviewed.³¹² Compounds isolated from SB have been shown to have antiviral and Nrf2-promoting antioxidant properties.³¹³ SB has shown utility in downregulation of NLRP3 inflammasomes,^{314,315} antimycobacterial and anti-inflammatory effects in macrophage infection,³¹⁶ and anti-H1N1 activity in vitro and in vivo through induction of IFN- γ producing cells.³¹⁷ Activity against H1N1 and H3N2 infected cells has been shown to be associated with upregulation of type 1 interferons.³¹⁸

In children with acute lymphocytic leukemia, administration of SB extract yielded increased production of IFN γ in peripheral blood lymphocytes (PBLs), and reduced TNF α and IL-10 production in bone marrow cells (BMC), in all patients.³¹⁹ The increase in immune surveillance (increased IFN γ) and downregulation of inflammation (reduced TNF α) constitute a potentially useful dual effect. Other phytochemicals similar to SB have been identified that block the entry of SARS-CoV into host cells.³²⁰

c. *Glycyrrhiza glabra* (Licorice root) - *Glycyrrhiza glabra*, common name licorice root, has a long history of use in Western herbal medicine for viral infections and in traditional Chinese medicine (TCM) as a key ingredient for pandemic formulas. It was a component in TCM formulas for SARS-CoV-1 prevention and treatment. Along with astragalus, it is the most frequently used botanical in TCM formulas for SARS-CoV-2 prevention in China.³²¹ Multiple clinical trials have demonstrated its effectiveness as a part of TCM formulas for CoV-1 and H1N1.³²² Numerous in-vitro studies have shown the major active constituent of licorice, glycyrrhizin, to be effective against SARS-CoV-1.³²² The Th1 promoting properties of licorice may contribute to its antiviral action and have been reviewed.³²³

A 2003 study published in *Lancet* looking at two clinical isolates of coronavirus from patients with SARS-CoV-1 identified glycyrrhizin to be the most active component of licorice in inhibiting viral replication as compared to ribavirin, 6-azauridine, pyrazofurin, and mycophenolic acid.³²⁴

A preprint molecular docking study suggests that the major active constituent, glycyrrhizin, can bind the ACE2 receptor, and therefore may have anti-SARS-CoV-2 activity.³²⁵

Licorice is considered a botanical of low toxic potential and has been safely used in Western and Eastern herbal medicine for millennia. However, excessive use can exert an aldosterone-like effect resulting in potassium wasting. Prescribing glycyrrhizin in individuals on potassium wasting medications may result in hypokalemia.³²⁶ It's also important to note that SARS-CoV-2 itself has been associated with potassium wasting,³²⁷ as is hydroxychloroquine, a drug gaining some renown as a potential COVID19 therapeutic, especially early in the disease process.³²⁸ Clinical considerations for patients with an increased risk for cardiac arrhythmias, either secondary to acquired conditions or co-morbidities or consequent to inherited syndromes, have been reviewed.³²⁹ Thus, while glycyrrhizin may be a very important COVID19 intervention, serum potassium should be monitored to avoid hypokalemia in vulnerable individuals.

Note that while DGL has substantial clinical research for such conditions as gastric ulcers, this form is not appropriate for COVID-19 as it is deglycyrrhizinized, i.e., the antiviral constituent has been removed.

d. *Echinacea* spp. - Extracts of various species of echinacea have been used traditionally in North America for many years and are currently popular for the treatment of many types of upper respiratory infections. Recent studies have supported its use by demonstrating that echinacea extracts possess potent

pleomorphic antiviral activities. Direct viricidal activity has been demonstrated particularly against membrane containing viruses including coronaviruses by targeting membrane components, capsid proteins, and virus replication. In addition, reversal of the pro-inflammatory response of epithelial cells to viral infection, and reduction of excessive mucin secretion has also been observed.^{330,331}

Of possible particular utility in COVID-19 is a species of echinacea with a long history of use in Western herbal medicine: *Echinacea angustifolia*. Also known as narrow-leaved purple coneflower, this medicinal herb is native to North America. A particular standardized extract of echinacea was shown to upregulate IL-2 and IL-8 and downregulate TNF α and IL-6 gene expression.³³² An uncontrolled pilot study of this preparation in 36 adults with existing respiratory disorders (chronic bronchitis, respiratory insufficiency, or intrinsic asthma) found improved response to influenza vaccination and a substantial, statistically significant increase in IgG.³³³

Variation in extractions methods, errors in identification, and inconsistent choices in part of plant used present challenges in the clinical choice of echinacea products. Research on a particular extract cannot be reliably extrapolated to other products.

e. Th2 Dominance Inhibition - Understanding the complex dynamics of T cell polarization patterning has gone far beyond Mossman's original Th1/Th2 dichotomy.³³⁴ There are currently seven known maturation fates of naïve T cells, and immunologists no longer think of Th1 as inflammatory and Th2 as anti-inflammatory. In patients whose baseline function likely involves Th2 dominance, indicated by asthma, chronic sinusitis, allergies, or other known Th2-dominant disease processes, or in patients for whom there are other concerns about the prospect of a loss of adequate Th1 response early in the infection phase of illness, it may be useful to consider downregulating an overly exuberant Th2 response.

i. *Perilla* spp. - *Perilla* has been shown to downregulate Th2 dominance-based processes like allergic airway inflammation, seasonal allergic rhinoconjunctivitis, and asthma.^{335,336} Mechanistic studies suggest this effect is mediated by downregulation of Th2 effector cytokines, including most importantly (IL-4), the cytokine driving Th2-biased autocrine responses. *Perilla* has also been shown to inhibit platelet aggregation and thrombus formation.^{337,338} Dietary supplementation with *perilla* seed oil in patients with asthma suppressed the generation of leukotriene (LT) C4.³³⁹

ii. *Radix astragali* (Astragalus) - *Astragalus* has substantial Th2 inhibiting properties. As with *perilla*, *astragalus* significantly decreased intensity of Th2 dominance-based disease processes like rhinorrhea.³⁴⁰ Mechanistic studies have shown that *astragalus* downregulates Th2 cytokines and lowers the ratio of GATA3 (Th2 cell transcription factor) to Tbet (Th1 cell transcription factor).³⁴¹⁻³⁴³ *Astragalus* also upregulates the formation of NK cells in peripheral blood mononuclear cells (PBMCs) from SLE patients.³⁴⁴

4. Anti-Inflammatory Support

Inhibition of the NLRP3 inflammasome and NF κ B are central to this task.

a. Potassium - Maintaining blood potassium levels is important, to prevent potassium cellular efflux, which upregulates inflammasome assembly.⁴²

COVID-19 drug therapy guidance published on April 8, 2020, from the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society states that hypokalemia should be corrected to >4.0 mEq/L and hypomagnesemia corrected to >2.0 mg/dL.³⁴⁵

b. *Curcuma longa* (Turmeric) - Curcuminoids are long used turmeric-derived compounds with well-documented pleotropic effects, including antiviral and anti-inflammatory activity.^{346,347}

As has been discussed, the aggressive virulence of SARS-CoV-2 may be driven in part by upregulation of NLRP3 leading to production of IL-1 β , IL-18 and pyroptotic cell death.³⁴⁸

Curcuminoids have been shown to specifically inhibit caspase-1 activation and IL-1 β secretion through suppressing LPS priming and NLRP3 activation.³⁴⁹

Regarding activity specific to SARS-CoV-2, recent prepublication molecular docking data suggest that the curcuminoids demethoxycurcumin and curcumin have viral replication inhibition potential against the main protease (Mpro) identified as likely involved in viral maturation and spread. Note that a number of other flavonoids demonstrated inhibition potential in the docking study, with the strongest and best potential SARS-CoV-2 Mpro inhibitors being: kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate.³⁵⁰

In another molecular docking study, curcumin showed effective inhibition of SARS-Cov-2 Spike viral glycoprotein binding to ACE2 receptor. While these data are clearly preliminary, the findings suggest the potential of curcumin to halt viral entry into host cells. Other effective flavonoids included hesperidin, with the highest binding affinity.³⁵¹

c. Bromelain - Many studies have documented efficacy of bromelain in reducing inflammation and inflammatory diseases. Clinical benefit has been shown in injuries, infections, respiratory tract diseases, arthritis, inflammatory bowel disease, etc. Of particular importance here is its documented ability to decrease tissue edema and inflammation.

Several studies have shown that bromelain is effective in respiratory conditions such as asthma, bronchitis, and sinusitis that are characterized by increased mucus production and inflammation. Spirometry before and after bromelain treatment demonstrated increased FEV1 and vital capacity, which were suggested by the researchers to be a result of bromelain's mucolytic activity.^{352,353}

Of particular interest here is the limited research showing that bromelain decreases cytokines. A placebo-controlled randomized clinical trial found that high-dose oral bromelain showed immunomodulation of both Th1- and Th2- cytokines.³⁵⁴

d. Resveratrol - Constituents of resveratrol have been shown to reduce inflammation via several mechanisms including downregulation of IL-6 and TNF α and promotion of Sirtuins.³⁵⁵⁻³⁵⁸ Crucial to the utility of resveratrol is its ability to inhibit the accumulation of acetylated α -tubulin caused by mitochondrial damage in macrophages stimulated by NLRP3-inflammasome induction. Inflammasome assembly is strongly induced by acetylated α -tubulin. Resveratrol upregulates SIRT2, a known deacetylator of α -tubulin.³⁵⁹⁻³⁶¹ The utility of resveratrol has been studied in SARS-CoV-1.³⁶² Resveratrol has been shown to protect lung epithelia against the effects of cigarette smoke by upregulating Nrf2 to promote GSH.³⁶³

The utility of resveratrol has been studied in a wide range of diseases including cardiovascular³⁶⁴ and metabolic inflammatory processes.³⁶⁵

e. Quercetin - See the quercetin discussion above.

f. Melatonin - See the melatonin discussion above.

g. Boswellia serrata (Boswellia) - Via a variety of mechanisms, boswellic acid (BA), an active constituent in *Boswellia serrata*, exerts a number of anti-inflammatory effects. BA was shown to potentially inhibit TGF β induced pulmonary fibrosis and 5-lipoxygenase in an animal model.³⁶⁶ BA has also been shown to significantly inhibit cyclooxygenase, NF κ B signaling and TNF α .^{367,368}

h. Sulforaphane - Sulforaphane is a well-studied anti-inflammatory phytochemical found in cruciferous vegetables that also inhibits NLRP3 inflammasome biology.^{369,370} Sulforaphane activates

the antioxidant Nrf2 pathway and drives significant anti-fibrotic activity benefit in both TGF β treated cell lines, and induced fibrosis in animal models.³⁷¹ Sulforaphane also upregulates GSH levels.^{372,373}

It is noteworthy that curcumin, resveratrol, quercetin, and berberine have all been shown to promote AMPK.³⁷⁴ AMPK is a promoter of SIRT2, also known to inhibit NLRP3 inflammasome assembly.²³

5. Anti-Oxidant Support

Patient GSH status can be supported with oral GSH (liposomal forms appear to offer better absorption), NAC, vitamin E, and selenium. In addition, GSH can be delivered by nebulizer or by IV. It may be appropriate to give both NAC and GSH, in service of supporting GSH status. When available, lab testing can support the clinician's monitoring of GSH levels.

NAC and GSH – Oral and Nebulized Delivery

Nebulized NAC and reduced GSH have a long history of clinical use by natural/ integrative/ functional/ holistic doctors for the treatment of COPD and other chronic inflammatory lung conditions. While there is substantial research support for the value of oral NAC and oral GSH in respiratory illnesses, the research to date on the nebulized delivery is limited but encouraging.

NAC—oral, IV and nebulized—has considerable research support for improving respiratory tract immunity, normalization of inflammation, helping reduce excessive mucous secretion and functioning as a mucolytic. A recent review well summarized its value in respiratory diseases:

Biological and pharmacological effects of NAC include improvement in rheological properties of mucus, reduction of excess mucin production, restoration of mucociliary clearance and production of sIgA, suppression of excess production of IgE and IgG4, destruction of biofilms and inhibition of their formation, suppression of adhesion of pathogenic bacteria to epithelial cells, antioxidant activity, regulation of the production of pro-inflammatory and profibrotic cytokines.³⁷⁵

While nebulized forms are likely more effective, oral NAC at 600 mg bid was shown in a controlled study of patients with COPD to significantly improved PaO₂, PaCO₂, wheezing, and dyspnea and decrease the need for nasal oxygen support.³⁷⁶

While most studies support this intervention, a clinical study on mechanically ventilated patients showed that while NAC was more effective than saline in decreasing mean secretion density the results were not statistically significant ($P = .087$), likely due to a small sample size (20 patients in each arm). However, despite small sample size, NAC was significantly effective at increasing O₂ saturation.³⁷⁷

A randomized, controlled study of IV NAC (50 mg/kg/day for three days) for 27 ICU patients with ALI/ARD demonstrated statistically significant improvement in oxygenation and decreased mortality.³⁷⁸

Normally, nebulized GSH would be recommended for respiratory inflammation. However, the high level of mucous secretion in COVID-19 could impair its ability to penetrate deeply enough into the lungs. Therefore, the authors recommend IV GSH, to protect both the lungs and also the heart from the damaging inflammation.

While there are a considerable number of controlled clinical studies on the various forms of NAC, there is a surprising dearth of such studies on IV GSH as an independent therapy. Virtually all existing studies examine the use of IV GSH in conjunction with drugs, especially chemotherapy agents. There are several studies showing modest benefit in Parkinson's disease, but virtually no other conditions we could find in PubMed.³⁷⁹

The research is clear that inhaled GSH substantially increases blood levels. A few controlled studies have shown modest benefit from inhaled GSH in cystic fibrosis and asthma.^{380,381}

Dosage Information

Other than research to date cited here, clinical research on nutritional substances in COVID-19 has not yet been done. All nutritional supports listed here have shown efficacy in human trials in other conditions. Dosages recommended here reflect the well over 100 years of combined clinical experience and judgement of the authors.

Regarding Pregnancy and the five Targets of Support

Safety and dosing recommendations of the compounds listed in the Five Targets of Support have not been established for pregnant women. While some, but not all, of the recommendations in the foundational Target and other Target areas may be safe during pregnancy (e.g. vitamin D, zinc, vitamin C, fish oil), appropriate doses of those nutrients should be determined on an individual basis by the patient's care provider.³⁸²

Data Collection Resources

As clinical experience and research on COVID-19 continue to emerge, more information will become available to inform clinical decisions about dose and form of vitamins, minerals, botanicals, and other substances. Helpful resources for data collection include the following:

1. The Helgott Institute IRB-approved online case registry, available to all clinicians: <https://redcap.nunm.edu/redcap/surveys/?s=PE3EHAYDT3>
Traditional, Complementary and Integrative Health and Medicine COVID-19 Support Registry
2. <https://www.milliehealth.com/covid-data>
3. The COVID-19 Universal Registry, Cure-19, is a public dataset registry. <https://www.cure19.org/>

Dual Role Substances

In considering potential choices for influencing patient immunological function, it is generally useful to consider favoring strategies that support both the goal of efficient immune surveillance and also the goal of quieting excessive inflammatory activation. These may offer the advantage of efficient anti-pathogenic immunological activity, while also providing anti-inflammatory functions, so that inflammatory cytokine upregulation that comes with immune response to the virus does not move the patient high enough on the vertical axis of Figure 4 to increase their risk of expressing cytokine storm, sepsis, ARDS or other potential morbidity or mortality. For example, vitamin D inhibits activation of the inflammatory protein complex NFkB.³⁸³ Vitamin D is also necessary for the formation of macrophage lysosomal enzymes, without which the macrophages can't kill phagocytized pathogens.¹⁹⁶

Because many patients with COVID-19 die of complications driven by excessively intense upregulation of inflammatory mechanisms, it is essential to consider that any tactic deployed solely to create an inflammatory adjuvant may carry with it a greater risk than tactics that function in the dual roles of supporting anti-pathogenic efficiency and downregulation of inflammatory response. Further discernment is useful between substances whose anti-pathogenic activation is primarily a consequence of upregulation of inherently inflammatory mechanisms, via upregulation of NFkB and cytokines like TNF α , IL-1 β , IL-6, and IL-8, versus substances whose anti-pathogenic activity relies on upregulation of immune-directing cytokines like IL-12 and IFN γ , with the consequences of activation yielding efficiencies reviewed elsewhere in this paper.

Substances Normal to the Body

In the overall clinical endeavor, it is likely useful to consider favoring the clinical application of substances that are normal to the body, such as GSH, NAC, vitamins D, A, and C, and zinc.

Summary

Though much is yet to be understood about the SARS-CoV-2 virus and COVID-19, substantial knowledge of the underlying immunology and clinical tools that apply to therapeutic targets in the underlying immunology provide a basis for clinical application, careful observation, and discernment of the needs of patients who seek support for favorable outcomes in the context of COVID-19. A phased functional approach, based on attention to the time course of the disease process, may provide a useful basis for engaging the clinical process with these patients.

Appendix I. Drug – Nutrient Interactions

Nutraceutical/ Botanical	Significant Concern	Theoretical/Minor Concern
Vitamin D		- Steroids, phenobarbital and dilantin can interfere with vitamin D metabolism - Orlistat and cholestyramine may interfere with vitamin D absorption
Vitamin A	Warfarin activity may be affected by Vitamin A	- Retinoid medications and other products containing vitamin A may interact with each other - Neomycin, orlistat, and cholestyramine may interfere with vitamin A absorption
Vitamin C	Warfarin activity may be affected by Vitamin C	- Vitamin C may increase aluminum absorption from antacids - Vitamin C may decrease exogenous estrogen metabolism - Vitamin C may decrease fluphenazine concentrations - Large doses of vitamin C may reduce half-life of HIV protease inhibitors
Zinc		- Zinc may decrease absorption of some antibiotics when taken at same time - Zinc may increase side effects of cisplatin - Zinc may decrease the absorption of penicillamine - Amiloride may increase amount of zinc in body
Melatonin		Possible interactions with warfarin, nifedipine and immune suppressing drugs.
Quercetin	Quercetin may affect medications metabolized by CYP2C8, CYP2D6, CYP3A4, and P-glycoprotein substrates	- Quercetin may decrease the effectiveness of some antibiotics - Quercetin may increase concentrations of cyclosporine
Fish Oil		Fish oil may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding
N-Acetyl Cysteine		Caution in those with a sulfur sensitivity
Glutathione		Caution in those with a sulfur sensitivity
Astragalus		- Astragalus may decrease the effectiveness of cyclophosphamide and other immune suppressants - Astragalus may decrease the excretion of lithium
Andrographis		- Andrographis may decrease blood pressure, taking with blood pressure medications may cause hypotension - Andrographis may decrease the effectiveness of immune suppressing medications - Andrographis may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding
Reishi		- Reishi may decrease blood pressure, taking with blood pressure medications may cause hypotension - High doses of reishi may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding
Berberine	Berberine may decrease metabolism of cyclosporine	Berberine may affect medications metabolized by CYP3A4
Baicalin		- Baicalin may decrease the effects of exogenous estrogen - Baicalin may decrease the excretion of lithium
Echinacea		- Echinacea might decrease caffeine metabolism - Echinacea may affect medications metabolized by CYP3A4 and CYP1A2 - Echinacea may decrease the effectiveness of immune suppressing medications
Goldenseal		- Goldenseal may decrease cyclosporine metabolism - Goldenseal may increase digoxin levels - Goldenseal may affect medications metabolized by CYP2D6, CYP3A4, and P-Glycoprotein substrates.
Curcumin		Curcumin may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding
Bromelain		- Bromelain might increase levels of amoxicillin - Bromelain may change levels of tetracyclines - Bromelain may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding.
Resveratrol		- Resveratrol may affect medications metabolized by CYP3A4. - Resveratrol may slow blood clotting, taking with other blood thinners may increase chances for bruising and bleeding.
Sulforaphane		Sulforaphane may affect medications metabolized by CYP1A2
Boswellia		None known

Acknowledgements

The authors wish to acknowledge the substantial conceptual contributions provided by Neil Alexis, PhD, professor of pediatrics, Director of the Applied Immunobiology Laboratory at UNC Chapel Hill, and PI of the Human Sample Biorepository at the UNC CEMALB. The authors also wish to acknowledge Laurie A. Hofmann, MPH, immediate past Chairwoman and Chief Executive Officer, Institute for Functional Medicine, for convening the group that led to the development of this paper.

Author Disclosure Statement

The authors declare no conflicts of interest.

References

- Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol*. 2020 Mar;38(1):1-9.
- Tan L, Wang Q, Zhang D, Ding J, Huang Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther*. 2020 Mar 27;5:33.
- Wang, X., Xu, W., Hu, G. et al. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. *Cell Mol Immunol* (2020).
- Chu, H. et al. Middle east respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. *J. Infect. Dis*. 213, 904–914 (2016).
- Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe*. 2016 Feb 10;19(2):181-93.
- COVID-19: protecting health-care workers. *Lancet*. 2020 Mar 21;395(10228):922.
- Luster AD. Chemokines – Chemotactic Cytokines that Mediate Inflammation. *N Engl J Med*. 1998 Feb 12;338(7):436-45.
- Barnes P, Karin M. Nuclear factor- κ B – a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med*. 1997 Apr 10;336(15):1066-71.
- Soehnlein O, Lindbom L. Phagocyte partnership during the onset and resolution of inflammation. *Nat Rev Immunol*. 2010 Jun;10(6):427-39.
- Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, Jiang B. Comorbidities and multi-organ injuries in the treatment of COVID-19. *Lancet*. 2020 Mar 21;395(10228):e52.
- Klinker MW, Lundy SK. Multiple mechanisms of immune suppression by B lymphocytes. *Mol Med*. 2012 Feb 10;18:123-37.
- Pinkerton JW, Kim RY, Robertson AAB, et al. Inflammasomes in the lung. *Mol Immunol*. 2017 Jun;86:44-55.
- Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics*. In press.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020 Feb 15;395(10223):497-506.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–62.
- Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A Nationwide Analysis. *Eur Respir J*. 2020 Mar 26. pii: 2000547.
- Brauer M. How much, how long, what, and where: air pollution exposure assessment for epidemiologic studies of respiratory disease. *Proc Am Thorac Soc*. 2010 May;7(2):111-5.
- Wooding DJ, Ryu MH, Li H, Alexis NE, Pena O, Carlsten C. Acute air pollution exposure alters neutrophils in never-smokers and at-risk humans. *Eur Respir J*. 2020 Apr 3;55(4). pii: 1901495.
- Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol*. 2020 Feb 28. pii: S1556-0864(20)30132-5.
- Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. Lille Intensive Care COVID-19 and Obesity study group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity* (Silver Spring). 2020 Apr 9.
- Dietz W, Santos-Burgoa C. Obesity and its Implications for COVID-19 Mortality. *Obesity* (Silver Spring). 2020 Apr 1.
- Furman D, Chang J, Lartigue L, Bolen CR, Haddad F, et al. Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. *Nat Med*. 2017 Feb;23(2):174-184.
- Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. *Nature*. 2012 Jan 18;481(7381):278-86.
- Leemans JC, Kors L, Anders HJ, Florquin S. Pattern recognition receptors and the inflammasome in kidney disease. *Nat Rev Nephrol*. 2014 Jul;10(7):398-414.
- Szabo G, Petrasek J. Inflammasome activation and function in liver disease. *Nat Rev Gastroenterol Hepatol*. 2015 Jul;12(7):387-400.
- Im H, Ammit AJ. The NLRP3 inflammasome: role in airway inflammation. *Clin Exp Allergy*. 2014 Feb;44(2):160-72.
- Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020 Mar 14;34(2). pii: 1.
- Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med*. 2020 Mar 27.
- Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. *JAMA Cardiol*. Published online March 27, 2020.
- Zhang Y, Xiao M, Zhang S, Zhang S, Li Y. Coagulopathy and Antiphospholipid Antibodies in Patients with COVID-19. *NEJM*. 4.8.20. [Prepublication]. DOI: 10.1056/NEJMc2007575
- Giwa AL, Desai A, Duca A. Novel 2019 coronavirus SARS-CoV-2 (COVID-19): An updated overview for emergency clinicians. *Emerg Med Pract*. 2020 May 1;22(5):1-28. Epub 2020 Mar 24.
- Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020 Mar 14;34(2). pii: 1.
- Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe Acute Respiratory Syndrome Coronavirus Viroprotein 3a Activates the NLRP3 Inflammasome. *Front Microbiol*. 2019 Jan 29;10:50.
- Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? *Ecancermedicalscience*. 2020; 14: 1023.
- Leemans JC, Kors L, Anders HJ, Florquin S. Pattern recognition receptors and the inflammasome in kidney disease. *Nat Rev Nephrol*. 2014 Jul;10(7):398-414.
- Li, S., Wang, C., Jou, Y. et al. SARS coronavirus papain-like protease induces Egr-1-dependent up-regulation of TGF- β 1 via ROS/p38 MAPK/STAT3 pathway. *Sci Rep* 2016 6, 25754.
- Artlett CM. The Role of the NLRP3 Inflammasome in Fibrosis. *Open Rheumatol J*. 2012;6:80-6.
- Liu RM, Gaston Pravia KA. Oxidative stress and glutathione in TGF-beta-mediated fibrogenesis. *Free Radic Biol Med*. 2010 Jan 1;48(1):1-15.
- Anathy V, Lahue KG, Chapman DG, Chia SB, Casey DT, et al. Reducing protein oxidation reverses lung fibrosis. *Nat Med*. 2018 Aug;24(8):1128-1135.
- Donath MY. When metabolism met immunology. *Nat Immunol*. 2013 May;14(5):421-2.
- Liston A, Masters SL. Homeostasis-altering molecular processes as mechanisms of inflammasome activation. *Nat Rev Immunol*. 2017 Mar;17(3):208-214.
- Ozkurede VU, Franchi L. Immunology in clinic review series; focus on autoinflammatory diseases: role of inflammasomes in autoinflammatory syndromes. *Clin Exp Immunol*. 2012 Mar;167(3):382-90.
- Doria A, et al. Autoinflammatory diseases: how to put the fire inside the body out? *Autoimmun Rev*. 2012 Nov;12(1):1-4.
- Doria A, et al. Autoinflammation and autoimmunity: bridging the divide. *Autoimmun Rev*. 2012 Nov;12(1):22-30.
- Zhang Y, Xiao M, Zhang S, Zhang S, Li Y. Coagulopathy and Antiphospholipid Antibodies in Patients with COVID-19. *NEJM*. 4.8.20. [Prepublication]. DOI: 10.1056/NEJMc2007575.
- Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020 Apr;8(4):420-422.
- Considerable mucus found in small airways of COVID-19 patients: expert. *XinhuaNet* 2020-02-27 14:39:47.
- Cheng OZ1, Palaniyar N. NET balancing: a problem in inflammatory lung diseases. *Front Immunol*. 2013 Jan 24;4:1.
- Ebrahimi F, Giaglis S, Hahn S, Blum CA, Baumgartner C, Kutz A. Markers of neutrophil extracellular traps predict adverse outcome in community-acquired pneumonia: secondary analysis of a randomised controlled trial. *Eur Respir J*. 2018 Apr 26;51(4). pii: 1701389.
- Kaplan MJ, Radic M. Neutrophil extracellular traps: double-edged swords of innate immunity. *J Immunol*. 2012 Sep 15;189(6):2689-95.
- Elaskalani O, Abdol Razak NB, Metharom P. Neutrophil extracellular traps induce aggregation of washed human platelets independently of extracellular DNA and histones. *Cell Commun Signal*. 2018 May 29;16(1):24.
- Stoiber W, Obermayer A, Steinbacher P, Krautgartner WD. The Role of Reactive Oxygen Species (ROS) in the Formation of Extracellular Traps (ETs) in Humans. *Biomolecules*. 2015 May 4;5(2):702-23.
- Fadini GP, Menegazzo L, Scattolini V, Gintoli M, Albiero M, Avogaro A. A perspective on NETosis in diabetes and cardiometabolic disorders. *Nutr Metab Cardiovasc Dis*. 2016 Jan;26(1):1-8.
- Kimball AS, Obi AT, Diaz JA, Henke PK. The Emerging Role of NETs in Venous Thrombosis and Immunothrombosis. *Front Immunol*. 2016 Jun 27;7:236.
- Saffarzadeh M, Juenemann C, Queisser MA, Lochnit G, Barreto G, Galuska SP, et al. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. *PLoS One*. 2012;7(2):e32366.
- Xu J1, Zhang X, Pelayo R, Monestier M, Ammollo CT, Semeraro F, Taylor FB, Esmon NL, Lupu F, Esmon CT. Extracellular histones are major mediators of death in sepsis. *Nat Med*. 2009 Nov;15(11):1318-21.

57. Lipinska-Gediga M. Neutrophils, NETs, NETosis - old or new factors in sepsis and septic shock? *Anaesthesiol Intensive Ther.* 2017;49(3):235-240.
58. Zawrotniak M, Kozik A, Rapala-Kozik M. Selected mucolytic, anti-inflammatory and cardiovascular drugs change the ability of neutrophils to form extracellular traps (NETs). *Acta Biochim Pol.* 2015;62(3):465-73.
59. Fuchs TA, Brill A, Wagner DD. Neutrophil extracellular trap (NET) impact on deep vein thrombosis. *Arterioscler Thromb Vasc Biol.* 2012 Aug;32(8):1777-83.
60. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD Jr, et al. Extracellular DNA traps promote thrombosis. *Proc Natl Acad Sci U S A.* 2010 Sep 7;107(36):15880-5.
61. Joshi MB, Lad A, Bharath Prasad AS, Balakrishnan A, Ramachandra L, Satyamoorthy K. High glucose modulates IL-6 mediated immune homeostasis through impeding neutrophil extracellular trap formation. *FEBS Lett.* 2013 Jul 11;587(14):2241-6.
62. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents.* 2020 Mar 29;105954.
63. Pedersen F, Waschki B, Marwitz S, Goldmann T, Kirsten A, et al. Neutrophil extracellular trap formation is regulated by CXCR2 in COPD neutrophils. *Eur Respir J.* 2018 Apr 12;51(4). pii: 1700970.
64. Hernandez ML, Mills K, Almond M, Todoric K, Aleman MM, Zhang H, et al. IL-1 receptor antagonist reduces endotoxin-induced airway inflammation in healthy volunteers. *J Allergy Clin Immunol.* 2015 Feb;135(2):379-85.
65. Sautia A, Moore FA, Moore EE. Postinjury Inflammation and Organ Dysfunction. *Crit Care Clin.* 2017 Jan;33(1):167-191.
66. Irwin MRI. Sleep and inflammation: partners in sickness and in health. *Nat Rev Immunol.* 2019 Nov;19(11):702-715.
67. Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. *Brain Behav Immun.* (2017) 64:208-19.
68. Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci USA.* (2012) 109(16):5995-9.
69. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! *Autoimmun Rev.* 2020 Mar 20;102523.
70. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci.* 2005 Oct;6(10):775-86.
71. Anderson GP. Interactions between corticosteroids and beta-adrenergic agonists in asthma disease induction, progression, and exacerbation. *Am J Respir Crit Care Med.* 2000 Mar;161(3 Pt 2):S188-96.
72. Temelkova-Kurktschiev T, Siegert G, Bergmann S, Henkel E, Koehler C, Jaross W, et al. Subclinical inflammation is strongly related to insulin resistance but not to impaired insulin secretion in a high risk population for diabetes. *Metabolism* (2002) 51(6):743-9.
73. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* (1999) 19(4):972-8.
74. Müller S, Martin S, Koenig W, Hanifi-Moghaddam P, Rathmann W, Haastert B, et al. Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-alpha or its receptors. *Diabetologia* (2002) 45(6):805-12.
75. Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. *J Am Coll Cardiol* (2006) 48(4):677-85.
76. Szic KS, Ndlovu MN, Haegeman G, Berghe WV. Nature or nurture: let food be your epigenetic medicine in chronic inflammatory disorders. *Biochem Pharmacol* (2010) 80(12):1816-32.
77. Fisher G, Hyatt TC, Hunter GR, Oster RA, Desmond RA, Gower BA. Effect of diet with and without exercise training on markers of inflammation and fat distribution in overweight women. *Obesity* (Silver Spring) (2011) 19(6):1131-6.
78. Nicklas BJ, Ambrosius W, Messier SP, Miller GD, Penninx BW, Loeser RF, et al. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *Am J Clin Nutr.* (2004) 79(4):544-51.
79. Shukla SD, Budden KF, Neal R, Hansbro PM. Microbiome effects on immunity, health and disease in the lung. *Clin Transl Immunology.* 2017 Mar 10;6(3):e133.
80. Ery D, Hrabce de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* (2015) 18(7):965-77.
81. Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host Microbe* (2017) 21(4):455-466.e4.
82. Andersen K, Kesper MS, Marschner JA, Konrad L, Ryu M, Kumar Vr S, et al. Intestinal dysbiosis, barrier dysfunction, and bacterial translocation account for CKD-related systemic inflammation. *J Am Soc Nephrol* (2017) 28(1):76-83.
83. de Jong PR, González-Navajas JM, Jansen NJ. The digestive tract as the origin of systemic inflammation. *Crit Care* (2016) 20(1):279.
84. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med.* 2014 Feb;20(2):159-66.
85. Dickson RP, Martinez FJ, Huffnagle GB. The role of the microbiome in exacerbations of chronic lung diseases. *Lancet.* 2014 Aug 23;384(9944):691-702.
86. Wienhold SM, Macri M, Nouailles G, Dietert K, Gurtner C, Gruber AD, et al. Ventilator-induced lung injury is aggravated by antibiotic mediated microbiota depletion in mice. *Crit Care.* 2018 Oct 29;22(1):282.
87. Paolucci EM, Loukov D, Bowdish DME, Heisz JJ. Exercise reduces depression and inflammation but intensity matters. *Biol Psychol.* 2018 Mar;133:79-84.
88. Muñoz-Cánoves P, Scheele C, Pedersen BK, Serrano AL. Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? *FEBS J.* 2013 Sep;280(17):4131-48.
89. Hervier B, Russick J, Cremer I, Vieillard V. NK Cells in the Human Lungs. *Front Immunol.* 2019 Jun 4;10:1263.
90. Abbas A, Lichtman AH, Pillai S. *Basic Immunology, Functions and Disorders of the Immune System.* 5th ed. Elsevier, 2015.
91. Zheng, M., Gao, Y., Wang, G. et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* (2020).
92. Yoshimura A, Naka T, Kubo M. SOCS proteins, cytokine signaling and immune regulation. *Nat Rev Immunol.* 2007 Jun;7(6):454-65.
93. Zhu J, Paul WE. CD4 T cells: fates, functions, and faults. *Blood.* 2008 Sep 1;112(5):1557-69.
94. Zhu J, Paul WE. Peripheral CD4+ T-cell differentiation regulated by networks of cytokines and transcription factors. *Immunol Rev.* 2010 Nov;238(1):247-62.
95. Kim HY, et al. The many paths to asthma: phenotype shaped by innate and adaptive immunity. *Nat Immunol.* 2010 Jul 11(7): 577-584.
96. Ziegler SF, Artis D. Sensing the Outside World: TSLP Regulates Barrier Immunity. *Nat Immunol.* 2010 Apr;11(4):289-93.
97. Minutti CM, Drube S, Zaiss DM, et al. Epidermal Growth Factor Receptor Expression Licenses Type-2 Helper T Cells to Function in a T Cell Receptor-Independent Fashion. *Immunity.* 2017 Oct 17; 47(4): 710-722.e6.
98. Kamide Y, Utsugi M, Mori M, et al. Intracellular glutathione redox status in human dendritic cells regulates IL-27 production and T-cell polarization. *Allergy.* 2011 Sep;66(9):1183-92.
99. Fraternali A, Paoletti MF, Magnani M, et al. Antiviral and Immunomodulatory Properties of New Pro-Glutathione (GSH) Molecules. *Curr Med Chem.* 2006;13(15):1749-55.
100. Fraternali A, Brundu S, Magnani M. Glutathione and glutathione derivatives in immunotherapy. *Biol Chem.* 2017 Feb 1;398(2):261-275.
101. Gould NS, Min E, Day BJ. Macropinocytosis of Extracellular Glutathione Ameliorates Tumor Necrosis Factor α Release in Activated Macrophages. *PLoS One.* 2011; 6(10): e25704.
102. Cottam EM, Whelband MC, Wileman T. Coronavirus NSP6 restricts autophagosome expansion. *Autophagy.* 2014 Aug;10(8):1426-41.
103. Harris J, De Haro SA, Master SS, Keane J, Roberts EA, et al. T Helper 2 Cytokines Inhibit Autophagic Control of Intracellular Mycobacterium tuberculosis. *Immunity.* 2007 Sep;27(3):505-17.
104. Cuervo AM, Macian F. Autophagy, nutrition and immunology. *Mol Aspects Med.* 2012 Feb;33(1):2-13.
105. Fougeray S, Pallet N. Mechanisms and biological functions of autophagy in diseased and ageing kidneys. *Nat Rev Nephrol.* 2015 Jan;11(1):34-45.
106. Kritas SK, Ronconi G, Caraffa A, Gallenga CE, Ross R, Conti P. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. *J Biol Regul Homeost Agents.* 2020 Feb 4;34(1). doi: 10.23812/20-Editorial-Kritas.
107. Shaik Y, Caraffa A, Ronconi G, Lessiani G, Conti P. Impact of polyphenols on mast cells with special emphasis on the effect of quercetin and luteolin. *Cent Eur J Immunol.* 2018;43(4):476-481.
108. Danielski LG, Giustina AD, Bonfante S, Barichello T, Petronilho F. The NLRP3 Inflammasome and Its Role in Sepsis Development. *Inflammation.* 2020 Feb;43(1):24-31.
109. Álvarez-Erriro D, Vento-Tormo R, Ballestar E. Genetic and Epigenetic Determinants in Autoinflammatory Diseases. *Front Immunol.* 2017 Mar 22;8:318.
110. Rathinam VAK, Zhao Y, Shao F. Innate immunity to intracellular LPS. *Nat Immunol.* 2019 May;20(5):527-533.
111. Belizário JE, Faintuch J, Garay-Malpartida M. Gut Microbiome Dysbiosis and Immunometabolism: New Frontiers for Treatment of Metabolic Diseases. *Mediators Inflamm.* 2018 Dec 9;2018:2037838.
112. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. *Nat Rev Immunol.* 2008 Jul;8(7):523-32.
113. Wang W, Ye L, Ye L, Li B, Gao B, Zeng Y, et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. *Virus Res.* 2007 Sep;128(1-2):1-8.
114. Biswas SK, Rahman I. Environmental toxicity, redox signaling and lung inflammation: the role of glutathione. *Mol Aspects Med.* 2009 Feb-Apr;30(1-2):60-76.
115. Morris D, Khurasany M, Nguyen T, Kim J, Guilford F, et al. Glutathione and infection. *Biochim Biophys Acta.* 2013 May;1830(5):3329-49.
116. Sido B, Braunstein J, Breitkreutz R, Herfarth C, Meuer SC. Thiol-mediated redox regulation of intestinal lamina propria T lymphocytes. *J Exp Med.* 2000;192(6):907-912.

117. Hadzic T, Li L, Cheng N, Walsh SA, Spitz DR, Knudson CM. The role of low molecular weight thiols in T lymphocyte proliferation and IL-2 secretion. *J Immunol*. 2005;175(12):7965–7972.
118. Oliver JM, Albertini DF, Berlin RD. Effects of glutathione-oxidizing agents on microtubule assembly and microtubule-dependent surface properties of human neutrophils. *J Cell Biol*. 1976;71(3):921–932.
119. Kuppner MC, Scharner A, Milani V, et al. Ilofamide impairs the allostimulatory capacity of human dendritic cells by intracellular glutathione depletion. *Blood*. 2003;102(10):3668–3674.
120. Atkuri, KR, Mantovani JJ, Herzenberg LA, Herzenberg LA. N-acetylcysteine - a safe antidote for cysteine/ glutathione deficiency. *Current Opinion in Pharmacology* (2007) 7(4):355–359.
121. Gibson KR, Winterburn TJ, Barrett F, Sharma S, MacRury SM, Megson IL. Therapeutic potential of N-acetylcysteine as an antiplatelet agent in patients with type-2 diabetes. *Cardiovasc*
122. Wang B, Yee Aw T, Stokes KY. Redox Biol. 2018 Apr;14:218–228. N-acetylcysteine attenuates systemic platelet activation and cerebral vessel thrombosis in diabetes. *Diabetol*. 2011 May 21;10:43.
123. Martinez de Lizarrondo S, Gakuba C, Herbig BA, Repessé Y, Ali C, et al. Potent Thrombolytic Effect of N-Acetylcysteine on Arterial Thrombi. *Circulation*. 2017 Aug 15;136(7):646–660.
124. Salamon S, Kramar B, Marolt TP, Poljsak B, Milisav I. Medical and Dietary Uses of N-Acetylcysteine. *Antioxidants* (Basel). 2019 Apr 28;8(5): pii: E111.
125. Todisco T, Polidori R, Rossi F, et al. Effect of N-acetylcysteine in subjects with slow pulmonary mucociliary clearance. *Eur J Respir Dis Suppl*. 1985;139:136–41.
126. Vayalil PK, Iles KE, Choi J, Yi AK, Postlethwait EM, Liu RM. Glutathione suppresses TGF-beta-induced PAI-1 expression by inhibiting p38 and JNK MAPK and the binding of AP-1, SP-1, and Smad to the PAI-1 promoter. *Am J Physiol Lung Cell Mol Physiol*. 2007 Nov;293(5):L1281–92.
127. Hazel Jardin, William MacNee, Kenneth Donaldson and Irfan Rahman. Molecular Mechanism of Transforming Growth Factor (TGF)-β1-induced Glutathione Depletion in Alveolar Epithelial Cells. *J Biol Chem* 2002 Jun 14;277(24):21158–66.
128. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol*. 2009 Mar;9(3):162–74.
129. Hamilos DL, Zelarney P, Mascali JJ. Lymphocyte proliferation in glutathione-depleted lymphocytes: direct relationship between glutathione availability and the proliferative response. *Immunopharmacology*. 1989 Nov-Dec;18(3):223–35.
130. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020. *MMWR Morb Mortal Wkly Rep*. ePub: 8 April 2020.
131. Pae M, Meydani SN, Wu D. The role of nutrition in enhancing immunity in aging. *Aging Dis*. 2012;3(1):91–129.
132. Sibaii H, El-Zayat SR, El-Shaheed AA, Mahfouz NN, Sallam SF, El Azma MH. The Hidden Function of Vitamin D. *Open Access Maced J Med Sci*. 2016;4(4):591–595.
133. Aiello A, Farzaneh F, Candore G, Caruso C, Davinelli S, et al. Immunosenescence and Its Hallmarks: How to Oppose Aging Strategically? A Review of Potential Options for Therapeutic Intervention. *Front Immunol*. 2019; 10: 2247.
134. Franceschi C, Garagnani P, Vitale G, Capri M, Salvioli S. Inflammaging and 'Garb-aging'. *Trends Endocrinol Metab*. 2017 Mar;28(3):199–212.
135. McGonagle D, Sharifa K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmunity Reviews* (2020).
136. Nicholls JM, Poon LL, Lee KC, Ng WF, Lai ST, Leung CY. Lung pathology of fatal severe acute respiratory syndrome. *Lancet*. 2003 May 24;361(9371):1773–8.
137. Sargiacomo C, Sotgia F, Lisanti MP. COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection? *Aging* (Albany NY). 2020 Mar 30.
138. Tzilav V, Boursos E, Barbayianni I, Karampitsakos T, Kourtidou S, Ntassiou M, et al. Vitamin D prevents experimental lung fibrosis and predicts survival in patients with idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther*. 2019 Apr;55:17–24.
139. Alexis NE, Lay JC, Zhou H, Kim CS, Hernandez ML, Kehrl H, et al. The glutathione-S-transferase mu 1 (GSTM1) null genotype and increased neutrophil response to low-level ozone (0.06 ppm). *J Allergy Clin Immunol*. 2013 Feb;131(2):610–2.
140. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: A review of empirical evidence. *Sleep Med Rev*. 2015 Aug;22:23–36.
141. Yazdi Z, Loukazadeh Z, Moghaddam P, Jalilolghadr S. Sleep Hygiene Practices and Their Relation to Sleep Quality in Medical Students of Qazvin University of Medical Sciences. *J Caring Sci*. 2016 Jun 1;5(2):153–60.
142. Jansson-Fröjmark M, Evander J, Alfnsson S. Are sleep hygiene practices related to the incidence, persistence and remission of insomnia? Findings from a prospective community study. *J Behav Med*. 2019;42(1):128–138.
143. Zhou, Y, Hou, Y, Shen, J, et al. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov* 6, 14 (2020).
144. Sayed RKA, Fernández-Ortiz M, Diaz-Casado ME, Aranda-Martínez P, Fernández-Martínez J, et al. Lack of NLRP3 Inflammasome Activation Reduces Age-Dependent Sarcopenia and Mitochondrial Dysfunction, Favoring the Prophylactic Effect of Melatonin. *J Gerontol A Biol Sci Med Sci*. 2019 Oct 4;74(11):1699–1708.
145. Che H, Wang Y, Li H, Li Y, Sahil A, et al. Melatonin alleviates cardiac fibrosis via inhibiting lncRNA MALAT1/miR-141-mediated NLRP3 inflammasome and TGF-β1/Smads signaling in diabetic cardiomyopathy. *FASEB J*. 2020 Feb 17.
146. Bonomini F, Dos Santos M, Veronesi FV, Rezzani R. Inflammasome Modulation by Melatonin Supplementation in Chronic Pristane-Induced Lupus Nephritis. *Int J Mol Sci*. 2019 Jul 15;20(14): pii: E3466.
147. Wu HM, Xie QM, Zhao CC, Xu J, Fan XY, Fei GH. Melatonin biosynthesis restored by CpG oligodeoxynucleotides attenuates allergic airway inflammation via regulating NLRP3 inflammasome. *Life Sci*. 2019 Dec 15;239:117067.
148. Panossian A, Wikman G. Effects of Adaptogens on the Central Nervous System and the Molecular Mechanisms Associated with Their Stress-Protective Activity. *Pharmaceuticals* (Basel). 2010 Jan 19;3(1):188–224.
149. Liao LY, He YF, Li L, Meng H, Dong YM, Yi F, Xiao PG. A preliminary review of studies on adaptogens: comparison of their bioactivity in TCM with that of ginseng-like herbs used worldwide. *Chin Med*. 2018 Nov 16;13:57.
150. Panossian A, Hambardzumyan M, Hovhannissyan A, Wikman G. The adaptogens rhodiola and schizandra modify the response to immobilization stress in rabbits by suppressing the increase of phosphorylated stress-activated protein kinase, nitric oxide and cortisol. *Drug Target Insights*. 2007;2:39–54.
151. Panossian A, Wikman. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Curr Clin Pharmacol*. 2009 Sep;4(3):198–219.
152. Salve J, Pate S, Debnath K, Langade D. Adaptogenic and Anxiolytic Effects of Ashwagandha Root Extract in Healthy Adults: A Double-blind, Randomized, Placebo-controlled Clinical Study. *Cureus*. 2019 Dec 25;11(12):e6466.
153. Worthen M, Cash E. Stress Management. [Updated 2019 Jun 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK513300/>
154. Dusek JA, Benson H. Mind-body medicine: a model of the comparative clinical impact of the acute stress and relaxation responses. *Minn Med*. 2009 May; 92(5):47–50.
155. Hamer M, Endrighi R, Poole L. Physical activity, stress reduction, and mood: insight into immunological mechanisms. *Methods Mol Biol*. 2012;934:89–102.
156. Blázquez Martín, D., De La Torre, I., García-Zapirain, B., Lopez-Coronado, M., & Rodrigues, J. (2018). Managing and Controlling Stress Using mHealth: Systematic Search in App Stores. *JMIR mHealth and uHealth*, 6(5), e111.
157. Sims J. (1997). The evaluation of stress management strategies in general practice: an evidence-led approach. *The British journal of general practice: the journal of the Royal College of General Practitioners*, 47(422), 577–582.
158. Bloomgarden, ZT, Diabetes and COVID-19. *Journal of Diabetes*. 2020;12:347–349.
159. Brand-Miller JC, Stockmann K, Atkinson F, Petocz P, Denyer G. Glycemic index, postprandial glycemia, and the shape of the curve in healthy subjects: analysis of a database of more than 1000 foods. *The American Journal of Clinical Nutrition*, Volume 89, Issue 1, January 2009, Pages 97–105.
160. Zeevi D, Korem T, Zmora N, et al. Personalized Nutrition by Prediction of Glycemic Responses. *Cell*. 2015;163(5):1079–1094.
161. Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health—a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr*. 2008;87(1):258S–268S.
162. Livesey, G., & Tagami, H. (2009). Interventions to lower the glycemic response to carbohydrate foods with a low-viscosity fiber (resistant maltodextrin): meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2009 Jan;89(1):114–25.
163. Hätönen KA, Virtamo J, Eriksson JG, Sinkko HK, Sundvall JE, Valsta LM. Protein and fat modify the glycaemic and insulinemic responses to a mashed potato-based meal. *Br J Nutr*. 2011;106(2):248–253.
164. Rodbard D. Continuous Glucose Monitoring: A Review of Recent Studies Demonstrating Improved Glycemic Outcomes. *Diabetes Technol Ther*. 2017;19(S3):S25–S37.
165. Ricker MA, Haas WC. Anti-Inflammatory Diet in Clinical Practice: A Review. *Nutr Clin Pract*. 2017;32(3):318–325.
166. Glushakova O, Kosugi T, Roncal C, Mu W, Heinig M, Cirillo P, et al. Fructose induces the inflammatory molecule ICAM-1 in endothelial cells. *Journal of the American Society of Nephrology* : JASN, 19(9), 1712–1720.
167. Silva CA, Santos I, Shivappa N, Hebert JR, Crivellenti LC, Sartorelli DS. The role of food processing in the inflammatory potential of diet during pregnancy. *Revista de saude publica*, 53, 113.
168. Mozaffarian D, Rimm EB, King IB, Lawler RL, McDonald GB, Levy WC. trans fatty acids and systemic inflammation in heart failure. *Am J Clin Nutr*. 2004 Dec;80(6):1521–5.
169. O'Dwyer DN, Dickson RP, Moore BB. The Lung Microbiome, Immunity, and the Pathogenesis of Chronic Lung Disease. *Journal of immunology* (Baltimore, Md:1950), 196(12), 4839–4847.
170. Huffnagle GB, Kickson RP, Lukacs NW. The respiratory tract microbiome and lung inflammation: a two-way street. *Mucosal Immunology*, 10, 299–306.
171. Bradley KC, Finsterbusch K, Schnept D, Crotta S, Llorian M, Davidson, et al. Microbiota-Driven Tonic Interferon Signals in Lung Stromal Cells Protect from Influenza Virus Infection. *Cell Reports* 28, 245–256, July 2, 2019.
172. Di Pierro, F. A possible probiotic (S. salivarius K12) approach to improve oral and lung microbiotas and raise defenses against SARS-CoV-2. (2020) Minerva Medica Letter to the Editor.
173. Belkaid Y, Hand T W. Role of the microbiota in immunity and inflammation. *Cell*, 157(1), 121–141.

174. Blander JM, Longman RS, Iliev ID, Sonnenberg GF, Artis D. Regulation of inflammation by microbiota interactions with the host. *Nature immunology*, 18(8), 851–860.
175. Janeway CA Jr, Travers P, Walport M, et al. The mucosal immune system. New York: Garland Science; 2001.
176. Kumar Singh A, Cabral C, Kumar R, Ganguly R, Kumar Rana H, Gupta A, et al. Beneficial Effects of Dietary Polyphenols on Gut Microbiota and Strategies to Improve Delivery Efficiency. *Nutrients*, 11(9), 2216.
177. Enam F, Mansell TJ. Prebiotics: tools to manipulate the gut microbiome and metabolome. *J Ind Microbiol Biotechnol*. 2019;46(9–10):1445–1459.
178. Wilson AS, Koller KR, Ramaboli MC, et al. Diet and the Human Gut Microbiome: An International Review. *Dig Dis Sci*. 2020;65(3):723–740.
179. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therapeutic advances in gastroenterology*, 6(1), 39–51.
180. Zhang R, Chen L, Cao L, et al. Effects of smoking on the lower respiratory tract microbiome in mice. *Respir Res* 19, 253 (2018).
181. Rylance J, Kankwatira A, Nelson DE, Toh E, Day RB, Lin H, et al. Household air pollution and the lung microbiome of healthy adults in Malawi: a cross-sectional study. *BMC microbiology*, 16(1), 182.
182. Sun J. Vitamin D and mucosal immune function. *Current opinion in gastroenterology*, 26(6), 591–595.
183. McCullough FS, Northrop-Clewes CA, Thurnham DI. The effect of vitamin A on epithelial integrity. *Proc Nutr Soc*. 1999;58(2):289–293.
184. Hou Y, Wang L, Yi D, Wu G. N-acetylcysteine and intestinal health: a focus on its mechanism of action. *Front Biosci (Landmark Ed)*. 2015;20:872–891.
185. Wu D, Lewis ED, Pae M, Meydani SN. Nutritional Modulation of Immune Function: Analysis of Evidence, Mechanisms, and Clinical Relevance. *Front Immunol*. 2019 Jan 15;9:3160.
186. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhatta HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*. 2020 Apr 2;12(4). pii: E988.
187. Colotta F, Jansson B, Bonelli F. Modulation of inflammatory and immune responses by vitamin D. *J Autoimmun*. 2017 Dec;85:78–97.
188. Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA Jr, Kerley CP, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet Respir Med*. 2017 Nov;5(11):881–890.
189. Lee YH, Bae SC. Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: a meta-analysis. *Clin Exp Rheumatol*. 2016 Sep-Oct;34(5):827–833. Epub 2016 Apr 6.
190. Islam MA, Khandker SS, Alam SS, Kotyla P, Hassan R. Vitamin D status in patients with systemic lupus erythematosus (SLE): A systematic review and meta-analysis. *Autoimmun Rev*. 2019 Nov;18(11):102392.
191. Rak K, Bronkowska M. Immunomodulatory Effect of Vitamin D and Its Potential Role in the Prevention and Treatment of Type 1 Diabetes Mellitus-A Narrative Review. *Molecules*. 2018 Dec 24;24(1). pii: E53.
192. Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: An update. *Mult Scler Relat Disord*. 2017 May;14:35–45.
193. Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, Hormone, and Immunomodulator. *Nutrients*. 2018 Nov 3;10(11). pii: E1656.
194. Martineau AR, Jolliffe DA, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health Technol Assess*. 2019 Jan;23(2):1–44.
195. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017 Feb 15;356:i6583.
196. Hewison M. Vitamin D and immune function: an overview. *Proc Nutr Soc*. 2012 Feb;71(1):50–61.
197. Al Senaidy AM. Serum vitamin A and beta-carotene levels in children with asthma. *J Asthma*. 2009 Sep;46(7):699–702. PMID: 19728208;
198. <https://data.unicef.org/topic/nutrition/vitamin-a-deficiency/> (accessed 2020-04-09)
199. Fulgoni VL 3rd, Keast DR, Bailey RL, Dwyer J. Foods, fortificants, and supplements: Where do Americans get their nutrients? *J Nutr*. 2011 Oct;141(10):1847–54.
200. Leung WC, Hessel S, Méplan C, et al. Two common single nucleotide polymorphisms in the gene encoding beta-carotene 15,15'-monooxygenase alter beta-carotene metabolism in female volunteers. *FASEB J* (2009 Apr) 23 (4) 1041–1053.
201. Jee J, Hoet AE, Azevedo MP, Vlasova AN, Loerch SC, Pickworth CL, et al. Effects of dietary vitamin A content on antibody responses of feedlot calves inoculated intramuscularly with an inactivated bovine coronavirus vaccine. *Am J Vet Res*. 2013 Oct;74(10):1353–62.
202. Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of Vitamin A in the Immune System. *J Clin Med*. 2018 Sep 6;7(9). pii: E258
203. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr*. 2006 Feb;83(2):191–201. PMID: 16469975
204. Fawzi WW, Msamanga GI, Spiegelman D, Wei R, Kapiga S, Villamor E, et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med*. 2004 Jul 1;351(1):23–32.
205. Johansson S. Vitamin A and Osteoporosis: Experimental and Clinical Studies. Acta Universitatis Upsaliensis. *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine*, 1392 (2004) 65 pp.
206. Myhre AM, Carlsen MH, Bohn SK, Wold HL, Laake P, Blomhoff R. Water-miscible, emulsified, and solid forms of retinol supplements are more toxic than oil-based preparations. *Am J Clin Nutr*. 2003 Dec;78(6):1152–9.
207. Reifen R. Vitamin A as an anti-inflammatory agent. *Proc Nutr Soc*. 2002 Aug;61(3):397–400.
208. Shankar, AH, and Prasad, AS. Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr*. 1998 Aug;68(2 Suppl):447S–463S.
209. Haase, H, Rink L, Multiple impacts of zinc on immune function. *Metallomics*. (2014) Jul;6(7):1175–80
210. Haase, H, Rink L, Zinc Signals and immune function. *Biofactors* ((2014) Jan-Feb;40(1):27–40.
211. Dardenne, M. Zinc and immune function. *Eur J Clin Nutri*. 2002 Aug;56 Suppl 3:S20–3.
212. Chasapis, CT, Loutsidou AC, Spiliopoulou, CA, Stefanidou, ME. Zinc and human health: an update. *Arch Toxicol*. 2012 Apr;86(4):521–34.
213. Bach JF, Dardenne M. Thymulin, a Zinc-Dependent Hormone. *Med Oncol Tumor Pharmacother*. 1989;6(1):25–9.
214. Krenn BM, Gaudernak E, Holzer B, Lanke K, Van Kuppeveld FJM, Seipelt J. Antiviral Activity of the Zinc Ionophores Pyrrhione and Hinokitol against Picornavirus Infections. *Journal of Virology* Dec 2008, 83 (1) 58–64; DOI: 10.1128/JVI.01543-08
215. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog*. 2010 Nov 4;6(11):e1001176.
216. Zinc for the common cold. Cochrane Systematic Review (2013) 6. John Wiley and sons, Ltd
217. Kitabayashi C, Fukada T, Kanamoto M, Ohashi W, Hojyo S, Atsumi T, et al. Zinc suppresses Th17 development via inhibition of STAT3 activation. *Int Immunol*. 2010 May;22(5):375–86.
218. Ogura H, Murakami M, Okuyama Y, Tsuruoka M, Kitabayashi C, Kanamoto M, et al. Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction. *Immunity*. 2008 Oct 17;29(4):628–36.
219. Mocchegiani E, Costarelli L, Giacconi R, Cipriano C, Muti E, Tesi S, Malavolta M. Nutrient-gene interaction in ageing and successful ageing. A single nutrient (zinc) and some target genes related to inflammatory/immune response. *Mech. Ageing Dev*. 127, 517–525.
220. Fujihara J, Yasuda T, Kimura-Kataoka K, Takinami Y, Nagao M, Takeshita H. Association of SNPs in genes encoding zinc transporters on blood zinc levels in humans. *Leg Med (Tokyo)*. 2018 Jan;30:28–33.
221. Mocchegiani E, Romeo J, Malavolta M, Costarelli L, Giacconi R, Diaz LE, Marcos A. Zinc: dietary intake and impact of supplementation on immune function in elderly. *Age (Dordr)*. 2013 Jun;35(3):839–60.
222. Mariani E, Neri S, Cattini L, Mocchegiani E, Malavolta M, Dedoussis GV, et al. Effect of Zinc Supplementation on Plasma IL-6 and MCP-1 Production and NK Cell Function in Healthy Elderly: Interactive Influence of +647 MT1a and -174 IL-6 Polymorphic Alleles. *Exp Gerontol*. 2008 May;43(5):462–71.
223. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in COVID-19 patients. *Laryngoscope*. 2020 Apr 1.
224. Pisano M, Hilas O. Zinc and Taste Disturbances in Older Adults: A Review of the Literature. *Consult Pharm*. 2016 May;31(5):267–70.
225. Maggini, S.; Wintergerst, E.S.; Beveridge, S.; Hornig, D.H. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. *Br. J. Nutr*. 2007, 98, S29–S35.
226. Webb, A.L.; Villamor, E. Update: Effects of antioxidant and non-antioxidant vitamin supplementation on immune function. *Nutr. Rev*. 2007, 65, 181.
227. Bozonet, S.M.; Carr, A.C.; Pullar, J.M.; Vissers, M.C.M. Enhanced human neutrophil vitamin C status, chemotaxis and oxidant generation following dietary supplementation with vitamin C-rich SunGold kiwifruit. *Nutrients* 2015, 7, 2574–2588.
228. De la Fuente, M.; Ferrandez, M.D.; Burgos, M.S.; Soler, A.; Prieto, A.; Miquel, J. Immune function in aged women is improved by ingestion of vitamins C and E. *Can. J. Physiol. Pharmacol*. 1998, 76, 373–380.
229. Carr, A.C.; Maggini, S. Vitamin C and Immune Function *Nutrients* 2017, 9(11), 1211
230. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol Ther*. 2018 Sep;189:63–70.
231. Levine, M.; Dhariwal, K.R.; Welch, R.W.; Wang, Y.; Park, J.B. Determination of optimal vitamin C requirements in humans. *Am. J. Clin. Nutr*. 1995, 62, 1347S–1356S.
232. Carr, A.C.; Frei, B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. *Am. J. Clin. Nutr*. 1999, 69, 1086–1087.
233. Hemilä H. Vitamin C and infections. *Nutrients* 2017;9(4):E339.
234. Webb AL, Villamor E. Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function. *Nutrition Reviews* 2007; Vol. 65, issue 5:181–217.
235. May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. *Antioxid Redox Signal*. 2013 Dec 10;19(17):2068–83.

236. Fowler AA 3rd, Truitt JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. *JAMA*. 2019;322(13):1261–70.
237. ClinicalTrials.gov [internet] Bethesda (MD): National Library of Medicine (US) Identifier: NCT04264533, Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia. 2020, Feb 11.
238. Chu W. Hospital turns to high-dose vitamin C to fight coronavirus. [internet] 03-26-20.
239. Hemilä H, Chalker, E. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis. *Nutrients* 2019, 11, 708.
240. Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM, et al. Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model. *J Agric Food Chem*. 2014 Aug 13;62(32):8085–93.
241. Chiow KH, Phoon MC, Putti T, Tan BK, Chow VT. Evaluation of antiviral activities of Houttuynia cordata Thunb. extract, quercetin, quercitrin and cinanserin on murine coronavirus and dengue virus infection. *Asian Pac J Trop Med*. 2016 Jan;9(1):1–7.
242. Jo S, Kim H, Kim S, Shin DH, Kim MS. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. *Chem Biol Drug Des*. 2019 Dec;94(6):2023–2030.
243. Smith M, Smith JC. Repurposing Therapeutics for COVID-19: Supercomputer-Based Docking to the SARS-CoV-2 Viral Spike Protein and Viral Spike Protein-Human ACE2 Interface. *ChemRxiv*. Preprint.
244. Norling LV, Serhan CN. Profiling in resolving inflammatory exudates identifies novel anti-inflammatory and pro-resolving mediators and signals for termination. *J Intern Med*. 2010 Jul;268(1):15–24.
245. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. *J Clin Invest*. 2018 Jul 2;128(7):2657–2669.
246. Lopategi A, Flores-Costa R, Rius B, López-Vicario C, Alcaraz-Quiles J, Titos E, Clària J. Frontline Science: Specialized proresolving lipid mediators inhibit the priming and activation of the macrophage NLRP3 inflammasome. *J Leukoc Biol*. 2019 Jan;105(1):25–36.
247. Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, Liu JP. Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. *Chin J Integr Med*. 2020 Apr;26(4):243–250.
248. Ding Y, Chen L, Wu W, Yang J, Yang Z, Liu S. Andrographolide inhibits influenza A virus-induced inflammation in a murine model through NF- κ B and JAK-STAT signaling pathway. *Microbes Infect*. 2017 Dec;19(12):605–615.
249. Panraksa P, Ramphan S, Khongwichit S, Smith DR. Activity of andrographolide against dengue virus. *Antiviral Res*. 2017 Mar;139:69–78.
250. Li F, Lee EM, Sun X, Wang D, Tang H, Zhou GC. Design, synthesis and discovery of andrographolide derivatives against Zika virus infection. *Eur J Med Chem*. 2020 Feb 1;187:111925.
251. Wintachai P, Kaur P, Lee RC, Ramphan S, Kuadkitkan A, Wikan N, et al. Activity of andrographolide against chikungunya virus infection. *Sci Rep*. 2015 Sep 18;5:14179.
252. Saxena RC, Singh R, Kumar P, Yadav SC, Negi MP, Saxena VS, et al. A randomized double blind placebo controlled clinical evaluation of extract of *Andrographis paniculata* (KalmCold) in patients with uncomplicated upper respiratory tract infection. *Phytomedicine*. 2010 Mar;17(3–4):178–85.
253. Gabrielian ES, Shukarian AK, Goukasova GI, Chandanian GL, Panossian AG, Wikman G, Wagner H. A double blind, placebo-controlled study of *Andrographis paniculata* fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. *Phytomedicine*. 2002 Oct;9(7):589–97.
254. Thamlakitkul V, Dechatiwongse T, Theerapong S, Chantrakul C, Boonroj P, Punkrut W, et al. Efficacy of *Andrographis paniculata*, Nees for pharyngotonsillitis in adults. *J Med Assoc Thai*. 1991 Oct;74(10):437–42.
255. Sheeja K, Kuttan G. Modulation of Natural Killer Cell Activity, Antibody-Dependent Cellular Cytotoxicity, and Antibody-Dependent Complement-Mediated Cytotoxicity by *Andrographolide* in Normal and Ehrlich Ascites Carcinoma-Bearing Mice. *Immunopharmacol Immunotoxicol*. 2006;28(3):443–57.
256. Gupta S, Mishra KP, Ganju L. Broad-spectrum antiviral properties of andrographolide. *Arch Virol*. 2017 Mar;162(3):611–623.
257. Parichatikanond W, Suthisaisang C, et al. Study of anti-inflammatory activities of the pure compounds from *Andrographis paniculata* (burm.f.) Nees and their effects on gene expression. *Int Immunopharmacol*. 2010 Nov;10(11):1361–73.
258. Ellan K, Thayan R, Raman J, Hidari KIPJ, Ismail N, Sabaratnam V. Anti-viral activity of culinary and medicinal mushroom extracts against dengue virus serotype 2: an in-vitro study. *BMC Complement Altern Med*. 2019 Sep 18;19(1):260.
259. Lim WZ, Cheng PG, Abdulrahman AY, Teoh TC. The identification of active compounds in *Ganoderma lucidum* var. antler extract inhibiting dengue virus serine protease and its computational studies. *J Biomol Struct Dyn*. 2019 Oct 24:1–16.
260. Sato N, Zhang Q, Ma CM, Hattori M. Anti-human immunodeficiency virus-1 protease activity of new lanostane-type triterpenoids from *Ganoderma sinense*. *Chem Pharm Bull (Tokyo)*. 2009 Oct;57(10):1076–80.
261. Donatini B. Control of oral human papillomavirus (HPV) by medicinal mushrooms, *Trametes versicolor* and *Ganoderma lucidum*: a preliminary clinical trial. *Int J Med Mushrooms*. 2014;16(5):497–8.
262. Zhang W, Tao J, Yang X, Yang Z, Zhang L, Liu H, et al. Antiviral effects of two *Ganoderma lucidum* triterpenoids against enterovirus 71 infection. *Biochem Biophys Res Commun*. 2014 Jul 4;449(3):307–12.
263. Kim YS, Eo SK, Oh KW, Lee C, Han SS. Antihyperlipidemic activities of acidic protein bound polysaccharide isolated from *Ganoderma lucidum* alone and in combinations with interferons. *J Ethnopharmacol*. 2000 Oct;72(3):451–8.
264. Xu Z1, Chen X, Zhong Z, Chen L, Wang Y. *Ganoderma lucidum* polysaccharides: immunomodulation and potential anti-tumor activities. *Am J Chin Med*. 2011;39(1):15–27.
265. Sun LX, Li WD, Lin ZB, Duan XS, Li XF, Yang N, et al. Protection against lung cancer patient plasma-induced lymphocyte suppression by *Ganoderma lucidum* polysaccharides. *Cell Physiol Biochem*. 2014;33(2):289–99.
266. Gao Y, Zhou S, Jiang W, Huang M, Dai X. Effects of ganopoly (a *Ganoderma lucidum* polysaccharide extract) on the immune functions in advanced-stage cancer patients. *Immunol Invest*. 2003 Aug;32(3):201–15.
267. Tsai CC, Yang FL, et al. Oligosaccharide and peptidoglycan of *Ganoderma lucidum* activate the immune response in human mononuclear cells. *J Agric Food Chem*. 2012 Mar;60(11):2830–7.
268. Chang CJ, Chen YY, Lai HC, et al. *Ganoderma lucidum* stimulates NK cell cytotoxicity by inducing NKG2D/NCR activation and secretion of perforin and granzyme. *Innate Immun*. 2014 Apr;20(3):301–11.
269. Pi CC, Chu CL, Lu CY, Zhuang YJ, Wang CL, Yu TH, et al. Polysaccharides from *Ganoderma formosanum* function as a YH1 adjuvant and stimulate cytotoxic T cell response in vivo. *Vaccine*. 2014 Jan 9;32(3):401–8.
270. Lin YL1, Lee SS, Hou SM, Chiang BL. Polysaccharide purified from *Ganoderma lucidum* induces gene expression changes in human dendritic cells and promotes T helper 1 immune response in BALB/c mice. *Mol Pharmacol*. 2006 Aug;70(2):637–44.
271. Lin CH, Hsiao YM, Ou CC, Lin YW, Chiu YL, Lue KH, et al. *Ganoderma* immunomodulatory protein, down-regulates tumor necrosis factor α -induced expression of matrix metalloproteinase 9 via NF- κ B pathway in human alveolar epithelial A549 cells. *J Agric Food Chem*. 2010 Nov 24;58(22):12014–21.
272. Batbayar S, Kim MJ, Kim HW. Medicinal mushroom *Lingzhi* or *Reishi*, *Ganoderma lucidum* beta-glucan induces Toll-like receptors and fails to induce inflammatory cytokines in NF- κ B inhibitor-treated macrophages. *Int J Med Mushrooms*. 2011;13(3):213–225.
273. Varghese FS, Thaa B, Amrun SN, Simarmata D, Rausalu K, Nyman TA, et al. The Antiviral Alkaloid Berberine Reduces Chikungunya Virus-Induced Mitogen-Activated Protein Kinase Signaling. *J Virol*. 2016 Oct 14;90(21):9743–9757.
274. Wang J, Wang L, Lou GH, Zeng HR, Hu J, Huang QW, et al. *Coptidis Rhizoma*: a comprehensive review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. *Pharm Biol*. 2019 Dec;57(1):193–225.
275. Varghese FS, Kaulinen P, Gläsker S, Bespalov M, Hanski L, Wennerberg K, et al. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. *Antiviral Res*. 2016 Feb;126:17–24.
276. Shin HB, Choi MS, Yi CM, Lee J, Kim NJ, Inn KS. Inhibition of respiratory syncytial virus replication and virus-induced p38 kinase activity by berberine. *Int Immunopharmacol*. 2015 Jul;27(1):65–8.
277. Dai Q, Zhang D, Yu H, Xie W, Xin R, Wang L, et al. Berberine Restricts Cocksackievirus B Type 3 Replication via Inhibition of c-Jun N-Terminal Kinase (JNK) and p38 MAPK Activation In Vitro. *Med Sci Monit*. 2017 Mar 25;23:1448–1455.
278. Wang YX, Yang L, Wang HQ, Zhao XQ, Liu T, Li YH, et al. Synthesis and Evolution of Berberine Derivatives as a New Class of Antiviral Agents against Enterovirus 71 through the MEK/ERK Pathway and Autophagy. *Molecules*. 2018 Aug 20;23(8). pii: E2084.
279. Wu Y, Li JQ, Kim YJ, Wu J, Wang Q, Hao Y. In vivo and in vitro antiviral effects of berberine on influenza virus. *Chin J Integr Med*. 2011 Jun;17(6):444–52.
280. Enkhtaiwan G, Kim DH, Park GS, Pandurangan M, Nicholas DA, Moon SH, et al. Berberine-piperazine conjugates as potent influenza neuraminidase blocker. *Int J Biol Macromol*. 2018 Nov;119:1204–1210.
281. Lee BH, Chaturanga K, Uddin MB, Weerathunga P, Kim MS, Cho WK. *Coptidis Rhizoma* extract inhibits replication of respiratory syncytial virus in vitro and in vivo by inducing antiviral state. *J Microbiol*. 2017 Jun;55(6):488–498.
282. Paolini R, Bernardini G, Molfetta R, Santoni A. NK cells and interferons. *Cytokine Growth Factor Rev*. 2015 Apr;26(2):113–20.
283. Perry AK, Chen G, Zheng D, Tang H, Cheng G. The host type I interferon response to viral and bacterial infections. *Cell Res*. 2005 Jun;15(6):407–22.
284. Zou K, Li Z, Zhang Y, Zhang HY, Li B, Zhu WL, et al. Advances in the study of berberine and its derivatives: a focus on anti-inflammatory and anti-tumor effects in the digestive system. *Acta Pharmacol Sin*. 2017 Feb;38(2):157–167.
285. Wang J, Wang L, Lou GH, Zeng HR, Hu J, Huang QW, et al. *Coptidis Rhizoma*: a comprehensive review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. *Pharm Biol*. 2019 Dec;57(1):193–225.
286. Lee CH, Chen JC. Berberine suppresses inflammatory agents-induced interleukin-1 β and tumor necrosis factor- α productions via the inhibition of I κ B degradation in human lung cells. *Pharmacol Res*. 2007 Sep;56(3):193–201.
287. Yang H, Zhu L, Gu Y, Kong X, Yan Liu, Chen M, et al. Berberine inhibits low shear stress-induced glycocalyx degradation via modulating AMPK and p47phox/Hyal2 signal pathway. *Eur J Pharmacol*. 2019 Aug 5;856:172413.
288. Xie Y, Liu X, Zhou P. In vitro Antifungal Effects of Berberine Against *Candida* spp. In Planktonic and Biofilm Conditions. *Drug Des Devel Ther*. 2020 Jan 9;14:87–101.

289. Jeong HW, Hsu KC, Kim JB, et al. Berberine suppresses proinflammatory responses through AMPK activation in macrophages. *Am J Physiol Endocrinol Metab*. 2009 Apr;296(4):E955-64.
290. Liemburg-Apers DC, Wagenaars JA, Smeitink JA, Willems PH, Koopman WJ. Acute stimulation of glucose influx upon mitochondrial dysfunction requires LKB1, AMPK, Sirt2 and mTOR-RAPTOR. *J Cell Sci*. 2016 Dec 1;129(23):4411-4423.
291. Xu Z, Feng W, Shen Q, Yu N, Yu K, Wang S, et al. Rhizoma Coptidis and Berberine as a Natural Drug to Combat Aging and Aging-Related Diseases via Anti-Oxidation and AMPK Activation. *Aging Dis*. 2017 Dec 1;8(6):760-777.
292. Jiang Y, Huang K, Lin X, Chen Q, Lin S, Feng X, et al. Berberine Attenuates NLRP3 Inflammasome Activation in Macrophages to Reduce the Secretion of Interleukin-1 β . *Ann Clin Lab Sci*. 2017 Nov;47(6):720-728.
293. Zhou H, Feng L, Xu F, Sun Y, Ma Y, Zhang X, et al. Berberine inhibits palmitate-induced NLRP3 inflammasome activation by triggering autophagy in macrophages: A new mechanism linking berberine to insulin resistance improvement. *Biomed Pharmacother*. 2017 May;89:864-874.
294. Nerstedt A, Johansson A, Andersson CX, Cansby E, Smith U, Mahlapuu M. AMP-activated protein kinase inhibits IL-6-stimulated inflammatory response in human liver cells by suppressing phosphorylation of signal transducer and activator of transcription 3 (STAT3). *Diabetologia*. 2010 Nov;53(11):2406-16.
295. Kim TS, Kang BY, Cho D, Kim SH. Induction of interleukin-12 production in mouse macrophages by berberine, a benzodioxoloquinolizine alkaloid, deviates CD4⁺ T cells from a Th2 to a Th1 response. *Immunology*. 2003 July; 109(3): 407-414.
296. Saha P, Bhattacharjee S, Sarkar A, et al. Berberine Chloride Mediates Its Anti-Leishmanial Activity via Differential Regulation of the Mitogen Activated Protein Kinase Pathway in Macrophages. *PLoS One*. 2011 Apr 5;6(4):e18467.
297. Kim TS, Kang BY, Cho D, Kim SH. Induction of interleukin-12 production in mouse macrophages by berberine, a benzodioxoloquinolizine alkaloid, deviates CD4⁺ T cells from a Th2 to a Th1 response. *Immunology*. 2003 July; 109(3): 407-414.
298. Evans CE. Hypoxia and HIF activation as a possible link between sepsis and thrombosis. *Thromb J*. 2019 Aug 14;17:16.
299. Evans CE, Humphries J, Mattock K, Saha P, Smith A. HIF1 signalling regulates venous thrombus resolution. *Thromb Res*. 2012 Dec;130(6):971-3.
300. Evans CE, Zhao YY. Impact of thrombosis on pulmonary endothelial injury and repair following sepsis. *Am J Physiol Lung Cell Mol Physiol*. 2017 Apr 1;312(4):L441-L451.
301. Lin S, Tsai SC, Lee CC, Wang BW, Liou JY, Shyu KG. Berberine inhibits HIF-1 α expression via enhanced proteolysis. *Mol Pharmacol*. 2004 Sep;66(3):612-9.
302. Pan Y, Shao D, Zhao Y, Zhang F, Zheng X, Tan Y, et al. Berberine Reverses Hypoxia-induced Chemoresistance in Breast Cancer through the Inhibition of AMPK- HIF-1 α . *Int J Biol Sci*. 2017 Jun 1;13(6):794-803.
303. Fu L, Chen W, Guo W, Wang J, Tian Y, Shi D, et al. Berberine Targets AP-2/ hTERT, NF- κ B/COX-2, HIF-1 α /VEGF and Cytochrome-c/Caspase Signaling to Suppress Human Cancer Cell Growth. *PLoS One*. 2013 Jul 15;8(7):e69240.
304. Zhang Q, Zhang C, Yang X, Yang B, Wang J, Kang Y, et al. Berberine inhibits the expression of hypoxia induction factor-1 α and increases the radiosensitivity of prostate cancer. *Diagn Pathol*. 2014 May 27;9:98.
305. Tsang CM, Cheung KC, Cheung YC, Man K, Lui VW, Tsao SW, Feng Y. Berberine suppresses Id-1 expression and inhibits the growth and development of lung metastases in hepatocellular carcinoma. *Biochim Biophys Acta*. 2015 Mar;1852(3):541-51.
306. Meng S, Wang LS, Huang ZQ, et al. Berberine ameliorates inflammation in patients with acute coronary syndrome following percutaneous coronary intervention. *Clin Exp Pharmacol Physiol*. 2012 May;39(5):406-11.
307. Cecil CE, Davis JM, Cech NB, Laster SM. Inhibition of H1N1 influenza A virus growth and induction of inflammatory mediators by the isoquinoline alkaloid berberine and extracts of goldenseal (*Hydrastis canadensis*). *Int Immunopharmacol*. 2011 Nov;11(11):1706-14.
308. Coutard B et al. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Research*. 2020;176:104742.
309. Peng M et al. Luteolin restricts dengue virus replication through inhibition of the proprotein convertase furin. *Antiviral Research*. 2017;143:176-185.
310. Wang ZL, Wang S, Kuang Y, Hu ZM, Qiao X, Ye M. A comprehensive review on phytochemistry, pharmacology, and flavonoid biosynthesis of *Scutellaria baicalensis*. *Pharm Biol*. 2018 Dec;56(1):465-484.
311. Zhao T, Tang H, Xie L, Zheng Y, Ma Z, Sun Q, Li X. *Scutellaria baicalensis* Georgi. (Lamiaceae): a review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. *J Pharm Pharmacol*. 2019 Sep;71(9):1353-1369.
312. Yang J, Yang X, Chu Y, Li M. Identification of Baicalin as an immunoregulatory compound by controlling T(H)17 cell differentiation. *PLoS One*. 2011 Feb 16;6(2):e17164.
313. Ji S, Li R, et al. Anti-H1N1 virus, cytotoxic and Nrf2 activation activities of chemical constituents from *Scutellaria baicalensis*. *J Ethnopharmacol*. 2015 Dec 24;176:475-84.
314. Li CG, Yan L, Mai FY, Shi ZJ, Xu LH, Jing YY, et al. Baicalin Inhibits NOD-Like Receptor Family, Pyrin Containing Domain 3 Inflammasome Activation in Murine Macrophages by Augmenting Protein Kinase A Signaling. *Front Immunol*. 2017 Oct 27;8:1409.
315. Liu Y, Jing YY, Zeng CY, Li CG, Xu LH, Yan L, et al. *Scutellaria baicalensis* Suppresses NLRP3 Inflammasome Activation in Macrophages and Protects Mice against Bacterial Sepsis. *Front Pharmacol*. 2018 Jan 9;8:975.
316. Zhang Q, Sun J, Wang Y, He W, Wang L, Zheng Y, et al. Antimycobacterial and Anti-inflammatory Mechanisms of Baicalin via Induced Autophagy in Macrophages Infected with *Mycobacterium tuberculosis*. *Front Microbiol*. 2017 Nov 2;8:2142.
317. Chu M, Xu L, et al. Role of Baicalin in Anti-Influenza Virus A as a Potent Inducer of IFN-Gamma. *Biomed Res Int*. 2015;2015:263630.
318. Li R, Wang L. Baicalin inhibits influenza virus A replication via activation of type I IFN signaling by reducing miR-146a. *Mol Med Rep*. 2019 Dec;20(6):5041-5049.
319. Orzechowska B, Chaber R, Wiśniewska A, et al. Baicalin from the extract of *Scutellaria baicalensis* affects the innate immunity and apoptosis in leukocytes of children with acute lymphocytic leukemia. *Int Immunopharmacol*. 2014 Dec;23(2):558-67.
320. Yi L, Li Z, Yuan K, Qu X, Chen J, Wang G. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *J Virol*. 2004 Oct;78(20):11334-9.
321. Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, Liu JP. Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. *Chin J Integr Med*. 2020 Apr;26(4):243-250.
322. Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A Review and Perspective. *Int J Biol Sci*. 2020; 16(10):1708-1717.
323. Wang L, Yang R, Yuan B, Liu Y, Liu C. The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. *Acta Pharm Sin B*. 2015 Jul;5(4):310-5.
324. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet*. 2003 Jun 14;361(9374):2045-6.
325. Chen H, Du Q. Potential Natural Compounds for Preventing SARS-CoV-2 (2019-nCoV) Infection. Preprints 2020, 2020010358.
326. Omar HR, Komarova I, El-Ghonemi M, Fathy A, Rashad R, Abdelmalak HD, et al. Licorice abuse: time to send a warning message. *Ther Adv Endocrinol Metab*. 2012 Aug;3(4):125-38.
327. Dong C, Li X, Song Q, Hu C, Su F, Dai J. Hypokalemia and Clinical Implications in Patients with Coronavirus Disease 2019 (COVID-19). medRxiv 2020.02.27.20028530.
328. Simpson TF, Kovacs RJ, Stecker EC. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19. *Cardiology Magazine* (American College of Cardiology). Mar 29, 2020.
329. Wu CI, Postema PG, Arbelo E, Behr ER, Bezzina CR, Napolitano C, et al. SARS-CoV-2, COVID-19 and inherited arrhythmia syndromes. *Heart Rhythm*. 2020 Mar 31. pii: S1547-5271(20)30285-X.
330. Hudson J, Vimalanathan S. (2011). Echinacea—A Source of Potent Antivirals for Respiratory Virus Infections. *Pharmaceuticals*, 4(7), 1019–1031.
331. McCann DA, Solco A, Liu Y, Macaluso F, Murphy PA, Kohut ML, Senchina DS. Cytokine- and interferon-modulating properties of Echinacea spp. root tinctures stored at -20 degrees C for 2 years. *J Interferon Cytokine Res*. 2007 May;27(5):425-36.
332. Dapas B, Dall'Acqua S, Bulla R, Agostinis C, Perissutti B, Invernizzi S, et al. Immunomodulation mediated by a herbal syrup containing a standardized Echinacea root extract: a pilot study in healthy human subjects on cytokine gene expression. *Phytomedicine*. 2014 Sep 25;21(11):1406-10.
333. Di Pierro F, Rapacioli G, Ferrara T, Togni S. Use of a standardized extract from *Echinacea angustifolia* (Polinacea[®]) for the prevention of respiratory tract infections. *Altern. Med. Rev.*, 17 (2012), pp. 36-41.
334. Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol*. 1989;7:145-73.
335. Chen ML, Wu CH, Hung LS, Lin BF. Ethanol Extract of *Perilla frutescens* Suppresses Allergen-Specific Th2 Responses and Alleviates Airway Inflammation and Hyperreactivity in Ovalbumin-Sensitized Murine Model of Asthma. *Evid Based Complement Alternat Med*. 2015;2015:324265.
336. Osakabe N, Takano H, Sanbongi C, Yasuda A, Yanagisawa R, Inoue K, Yoshikawa T. Anti-inflammatory and anti-allergic effect of rosmarinic acid (RA); inhibition of seasonal allergic rhinoconjunctivitis (SAR) and its mechanism. *Biofactors*. 2004;21(1-4):127-31.
337. Jang JY, Kim TS, Cai J, Kim J, Kim Y, Shin K. *Perilla* oil improves blood flow through inhibition of platelet aggregation and thrombus formation. *Lab Anim Res*. 2014 Mar;30(1):21-7.
338. Ishihara T, Okamoto I, et al. Inhibition of antigen-specific T helper type 2 responses by *Perilla frutescens* extract. *Arerugi*. 1999 Apr;48(4):443-50.
339. Okamoto M, Mitsunobu F, Ashida K, Mifune T, Hosaki Y, Tsugeno H, Harada S, Tanizaki Y, Kataoka M, Niiya K, Harada M. Effects of perilla seed oil supplementation on leukotriene generation by leukocytes in patients with asthma associated with lipometabolism. *Int Arch Allergy Immunol*. 2000 Jun;122(2):137-42.
340. Matkovic Z, Zivkovic V, Korica M, Plavec D, Pecanic S, Tudoric N. Efficacy and safety of *Astragalus membranaceus* in the treatment of patients with seasonal allergic rhinitis. *Phytother Res*. 2010 Feb;24(2):175-81.

341. Chen SM, Tsai YS, et al. Astragalus membranaceus modulates Th1/2 immune balance and activates PPAR γ in a murine asthma model. *Biochem Cell Biol*. 2014 Oct;92(5):397-405.
342. Qiu YY, Zhu JX, Bian T, Gao F, Qian XF, Du Q, et al. Protective effects of astragaloside IV against ovalbumin-induced lung inflammation are regulated/mediated by T-bet/GATA-3. *J Pharmacology*. 2014;94(1-2):51-9.
343. Li K, Chen Y, Jiang R, Chen D, Wang H, Xiong W, et al. Protective effects of astragaloside IV against ovalbumin-induced allergic rhinitis are mediated by T-box protein expressed in T cells/GATA-3 and forkhead box protein 3/retinoic acid-related orphan nuclear receptor γ t. *Mol Med Rep*. 2017 Aug;16(2):1207-1215.
344. Zhao XZ. Effects of Astragalus membranaceus and Tripterygium hypoglancum on natural killer cell activity of peripheral blood mononuclear in systemic lupus erythematosus. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 1992 Nov;12(11):669-71, 645.
345. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for Drug Interactions on QTc in Exploratory COVID-19 (Coronavirus Disease 2019) Treatment. *Circulation*. 4.8.20 [prepublication].
346. Hewlings SJ, Kalman DS. Curcumin: A Review of Its' Effects on Human Health. *Foods*. 2017 Oct 22;6(10). pii: E92.
347. Moghadamtousi SZ, Kadir HA, Hassandarvish P, Tajik H, Abubakar S, Zandi K. A review on antibacterial, antiviral, and antifungal activity of curcumin. *Biomed Res Int*. 2014;2014:186864.
348. Yang Y, Peng F, Wang R, Guan K, Jiang T, Xu G, et al. The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *J Autoimmun*. 2020 Mar 3:102434.
349. Yin H, Guo Q, Li X, Tang T, Li C, Wang H, et al. Curcumin Suppresses IL-1 β Secretion and Prevents Inflammation through Inhibition of the NLRP3 Inflammasome. *J Immunol*. 2018 Apr 15;200(8):2835-2846.
350. Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto, S. Potential Inhibitor of COVID-19 Main Protease (Mpro) From Several Medicinal Plant Compounds by Molecular Docking Study. Preprints 2020, 2020030226.
351. Utomo RY, Ikawati M, Meiyanto E. Revealing the Potency of Citrus and Galangal Constituents to Halt SARS-CoV-2 Infection. Preprints 2020, 2020030214.
352. Secor ER Jr, Carson WF IV, Cloutier MM, et al. Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murine model of allergic airway disease. *Cell Immunol* (2005) 237 68–75.
353. Rimoldi R, Ginesu F, Giura R. The use of bromelain in pneumological therapy. *Drugs Exp Clin Res* (1978) 4 55–66.
354. Müller S, März R, Schmolz M, Drewelow B, Eschmann K, Meiser P. Placebo-controlled randomized clinical trial on the immunomodulating activities of low- and high-dose bromelain after oral administration - new evidence on the antiinflammatory mode of action of bromelain. *Phytother Res*. 2013 Feb;27(2):199-204.
355. Shabani M, Sadeghi A, Hosseini H, Teimouri M, Babaei Khorzoughi R, Pasalar P, Meshkani R. Resveratrol alleviates obesity-induced skeletal muscle inflammation via decreasing M1 macrophage polarization and increasing the regulatory T cell population. *Sci Rep*. 2020 Mar 2;10(1):3791.
356. Sarubbo F, Esteban S, Miralles A, Moranta D. Effects of Resveratrol and other Polyphenols on Sirt1: Relevance to Brain Function During Aging. *Curr Neuropharmacol*. 2018 Jan 30;16(2):126-136.
357. Pan W, Yu H, Huang S, Zhu P. Resveratrol Protects against TNF- α -Induced Injury in Human Umbilical Endothelial Cells through Promoting Sirtuin-1-Induced Repression of NF-KB and p38 MAPK. *PLoS One*. 2016 Jan 22;11(1):e0147034.
358. Chen LZ, Yao L, Jiao MM, Shi JB, Tan Y, Ruan BF, Liu XH. Novel resveratrol-based flavonol derivatives: Synthesis and anti-inflammatory activity in vitro and in vivo. *Eur J Med Chem*. 2019 Aug 1;175:114-128.
359. Misawa T, Saitoh T, Akira S. Resveratrol inhibits the acetylated α -tubulin-mediated assembly of the NLRP3-inflammasome. *Int Immunol*. 2015 Sep;27(9):425-34.
360. Peredo-Escárcega AE, Rubio-Ruiz ME, et al. The Combination of Resveratrol and Quercetin Attenuates Metabolic Syndrome in Rats by Modifying the Serum Fatty Acid Composition and by Upregulating SIRT 1 and SIRT 2 Expression in White Adipose Tissue. *Evid Based Complement Alternat Med*. 2015;2015:474032.
361. Yang SJ, Lim Y. Resveratrol ameliorates hepatic metaflammation and inhibits NLRP3 inflammasome activation. *Metabolism*. 2014 May;63(5):693-701.
362. Li YQ, Li ZL, Zhao WJ, Wen RX, Meng QW, Zeng Y. Synthesis of stilbene derivatives with inhibition of SARS coronavirus replication. *Eur J Med Chem*. 2006 Sep;41(9):1084-9. Epub 2006 Jul 27.
363. Kode A, Rajendrasozhan S, Caito S, et al. Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. *Am J Physiol Lung Cell Mol Physiol*. 2008 Mar;294(3):L478-88.
364. Bonnefont-Rousselot D. Resveratrol and Cardiovascular Diseases. *Nutrients*. 2016 May 2;8(5). pii: E250.
365. Chaplin A, Carpené C, Mercader J. Resveratrol, Metabolic Syndrome, and Gut Microbiota. *Nutrients*. 2018 Nov 3;10(11). pii: E1651.
366. Ali, E.N., Mansour, S.Z. Boswellic acids extract attenuates pulmonary fibrosis induced by bleomycin and oxidative stress from gamma irradiation in rats. *Chin Med* 6, 36 (2011).
367. Siemoneit U, Hofmann B, Kather N, et al: Identification and functional analysis of cyclooxygenase-1 as a molecular target of boswellic acids. *Biochem Pharmacol* 75:503-513, 2008.
368. Wang H, Syrovets T, Kess D, et al: Targeting NF-kappa B with a natural triterpenoid alleviates skin inflammation in a mouse model of psoriasis. *J Immunol* 183:4755-4763, 2009.
369. Li S, Yang H, Chen X. Protective effects of sulforaphane on diabetic retinopathy: activation of the Nrf2 pathway and inhibition of NLRP3 inflammasome formation. *Exp Anim*. 2019 May 8;68(2):221-231.
370. Yang G, Yeon SH, Lee HE, Kang HC, Cho YY, Lee HS, Lee JY. Suppression of NLRP3 inflammasome by oral treatment with sulforaphane alleviates acute gouty inflammation. *Rheumatology (Oxford)*. 2018 Apr 1;57(4):727-736.
371. Kyung SY, Kim DY, Yoon JY, Son ES, Kim YJ, Park JW, Jeong SH. Sulforaphane attenuates pulmonary fibrosis by inhibiting the epithelial-mesenchymal transition. *BMC Pharmacol Toxicol*. 2018 Apr 2;19(1):13.
372. Sedlak TW, Nucifora LG, Koga M, Shaffer LS, Higgs C, Tanaka T. Sulforaphane Augments Glutathione and Influences Brain Metabolites in Human Subjects: A Clinical Pilot Study. *Mol Neuropsychiatry*. 2018 May;3(4):214-222.
373. Dias IH, Chapple IL, Milward M, Grant MM, Hill E, Brown J, Griffiths HR. Sulforaphane restores cellular glutathione levels and reduces chronic periodontitis neutrophil hyperactivity in vitro. *PLoS One*. 2013 Jun 24;8(6):e66407.
374. Kim I, He YY. Targeting the AMP-Activated Protein Kinase for Cancer Prevention and Therapy. *Front Oncol*. 2013 Jul 15;3:175.
375. Aldini G, Altomare A, Baron G, Vistoli G, Carini M, Borsani L, Sergio F. N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why. *Free Radic Res*. 2018 Jul;52(7):751-762.
376. Ansari SF, Memon M, Brohi N, Tahir A. N-acetylcysteine in the Management of Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *Cureus*, 11 (11), e6073 2019 Nov 5.
377. Masoompour SM, Anushiravani A, Tafaraj Norouz A. Evaluation of the Effect of Nebulized N-Acetylcysteine on Respiratory Secretions in Mechanically Ventilated Patients: Randomized Clinical Trial. *Iran J Med Sci*. 2015 Jul;40(4):309-15.
378. Moradi M, Mojtahedzadeh M, Mandegari A, Soltan-Sharifi MS, Najafi A, et al. The Role of glutathione-S-transferase Polymorphisms on Clinical Outcome of ALI/ARDS Patient Treated With N-acetylcysteine. *Respir Med Actions*, 103 (3), 434-41.
379. Hauser RA, Lyons KE, McClain T, Carter S, Perlmutter D. Randomized, double-blind, pilot evaluation of intravenous glutathione in Parkinson's disease. *Mov Disord*. 2009 May 15;24(7):979-83.
380. Calabrese C, Tosco A, Abete P, Carnovale V, Basile C, et al. Randomized, single blind, controlled trial of inhaled glutathione vs placebo in patients with cystic fibrosis. *J Cyst Fibros*. 2015 Mar;14(2):203-10.
381. Bagnato GF, Gulli S, De Pasquale R, Giacobbe O, Spataro G, Purrello D'Ambrosio F. Effect of inhaled glutathione on airway response to 'Fog' challenge in asthmatic patients. *Respiration*. 1999 Nov-Dec;66(6):518-21.
382. Ross AC, Cousins RJ, Caballero B, et.al. Modern Nutrition in Health and Disease, 11th edition. Chapter 52: *Nutrition in Pregnancy*. Wolters Kluwer Health, Lippincott Williams & Wilkins. 2014
383. Colotta F, Jansson B, Bonelli F. Modulation of inflammatory and immune responses by vitamin D. *J Autoimmun*. 2017 Dec;85:78-97.