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PathoBiochemistry-directed Guidelines for COVID-19

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Abstract. Patients with underlying health conditions are at risk for a poor outcome from Coronavirus disease 2019 (COVID-19). We investigated the pathobiochemistry of this observation to generate therapeutic guidelines. Using machine reasoning by the sci.AI system, facts were extracted and linked from publications available in nlm.nih.gov and Europe PMC to form the dataset which was validated by medical experts. Since preexisting chronic inflammation renders the acute inflammatory response to Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) excessive translating the SARS-CoV-2 infection into the clinical COVID-19 syndrome, we focus on therapeutic interventions that mitigate the immune response. In essence, from bench to bedside, as depicted in the Graphical Abstract, the clinical management of COVID-19 should aim at:
A. Control of excessive oxidant production.
B. Neutralization of excessive oxidants.
C. Upregulation of nitric oxide (NO) production.

Key words: COVID-19 therapy, oxidant, antioxidant, nitric oxide (NO), thrombosis

Background

In follow-up to our articles on the pathogenesis of Coronavirus disease 2019 (COVID-19), [1, 2] we have written this article focusing on its clinical applications.
When the body receives an insult, whether infectious or non-infectious, it responds with inflammation that is promoted by *the Prooxidant system* (PO) through cytokines, e.g. tumor necrosis factor-alpha (TNFα), generating the oxidant superoxide (O2-), a component of Reactive Oxygen Species (ROS), by NADPH oxidase. [3] However, oxidants can damage normal cells as well and *the Antioxidant system* (AO) defends the body by producing antioxidants. These two systems normally balance each other. The main antioxidants are glutathione (GSH) that neutralizes oxidants, and nitric oxide (NO) that inhibits its production through suppression of NADPH oxidase. [4] Both the PO and AO systems require the co-factor reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) which is produced by glucose-6-phosphate dehydrogenase (G6PD). [5]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects the body in two ways, as depicted in the Graphical Abstract (Fig.1):

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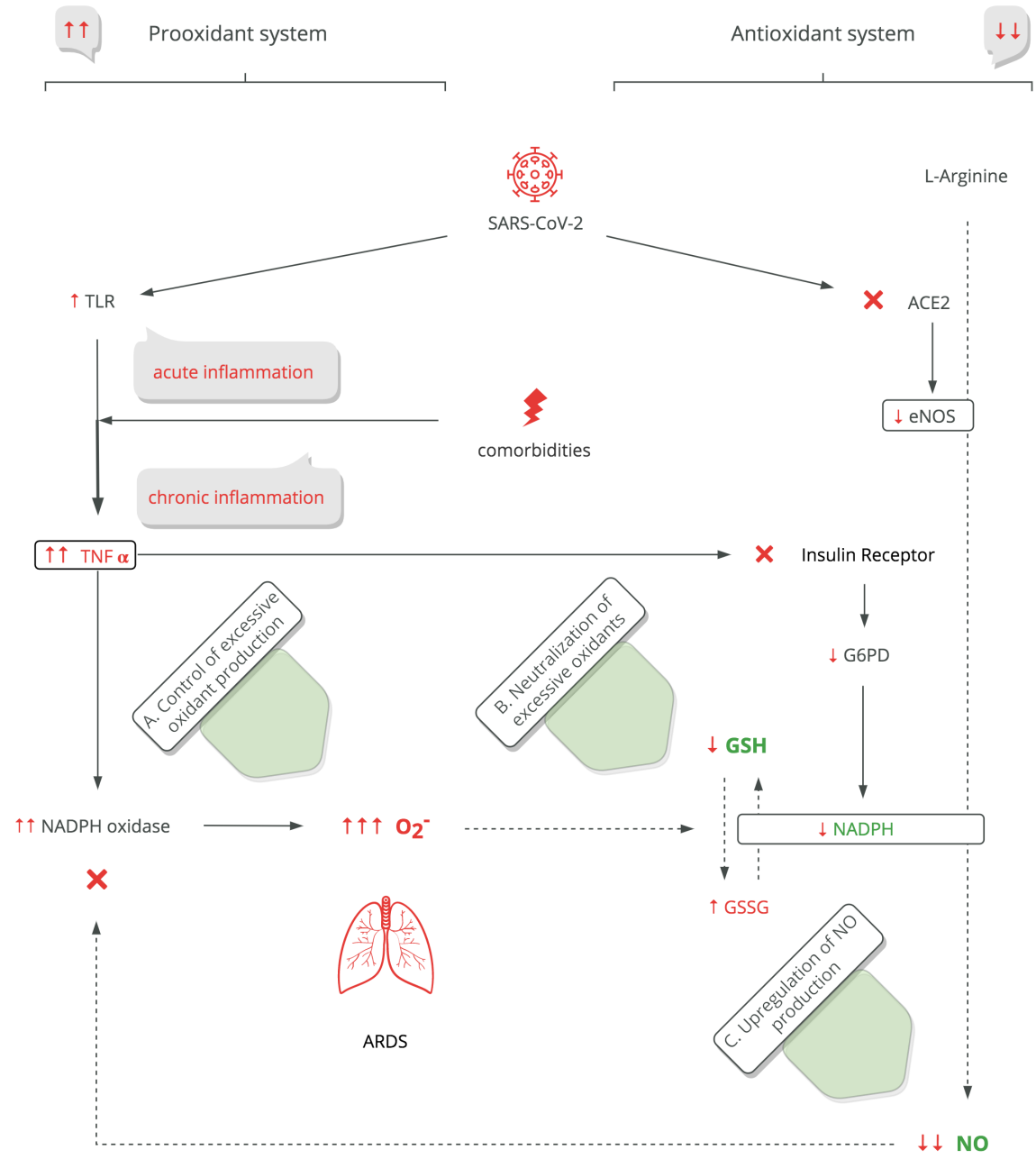

Fig. 1. Graphical Abstract

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1. Nonspecifically, as occurs for any pathogen, it triggers the PO system through activation of toll-like receptors (TLR), inducing *an acute inflammatory immune response*, [6] and
2. Specifically, it inhibits the AO system through suppression of the NO-producing angiotensin-converting enzyme 2 (ACE2) - endothelial nitric oxide synthase (eNOS) pathway. [7]

Chronic inflammation from non-infectious comorbidities, e.g. the metabolic syndrome, mediated through cytokines, continuously affects the body in two ways:

1. It triggers the PO system, and
2. It inhibits the AO system, through the inactivation of insulin receptors, [8] resulting in suppression of G6PD, and NADPH as a consequence.

Essentially, inflammation, whether it is acute or chronic, activates the PO and inhibits the AO systems. And preexisting chronic inflammation potentiates the acute inflammatory response to SARS-CoV-2. In addition, SARS-CoV-2 uniquely inhibits the AO system, rendering it excessive, also known as oxidative stress, cytokine storm, and systemic inflammatory response syndrome (SIRS). Excessive oxidants cause endothelial injury resulting in systemic edema and vasoconstriction. In the lungs, this manifests as Acute Respiratory Distress Syndrome (ARDS). [9]

Translating this into clinical practice, below, after describing our methods, we report our results and discuss the key pathobiochemical points of COVID-19 pathogenesis and their clinical applications.

Methods

We used the sci.AI machine reasoning system to operate on publicly available datasets from nlm.nih.gov and Europe PMC. The process consisted of several steps. The first step was to arbitrarily recognize universal biochemical entities and how they relate to each other. The second step was to build a subset of findings that appear to be relevant to COVID-19 pathogenesis. We progressively refined the knowledge and, ultimately, in the last step, linked these excerpts to synthesize pathobiochemical pathways to help explain the management of COVID-19.

Results and Discussion

Basic life processes require glucose metabolism, through oxidation, into energy, in the form of adenosine triphosphate (ATP). As depicted in Fig.2, during *metabolic oxidative processes*, electrons are transferred forming oxidants as a normal byproduct, and this occurs in up to 2% of daily oxygen (O2) consumption. [10] During *inflammation*, oxidants are produced intentionally as part of a normal immune response. However, increased oxidant production and/or its decreased neutralization result in harmful oxidative excess. There are several exogenous and endogenous factors that affect this condition.

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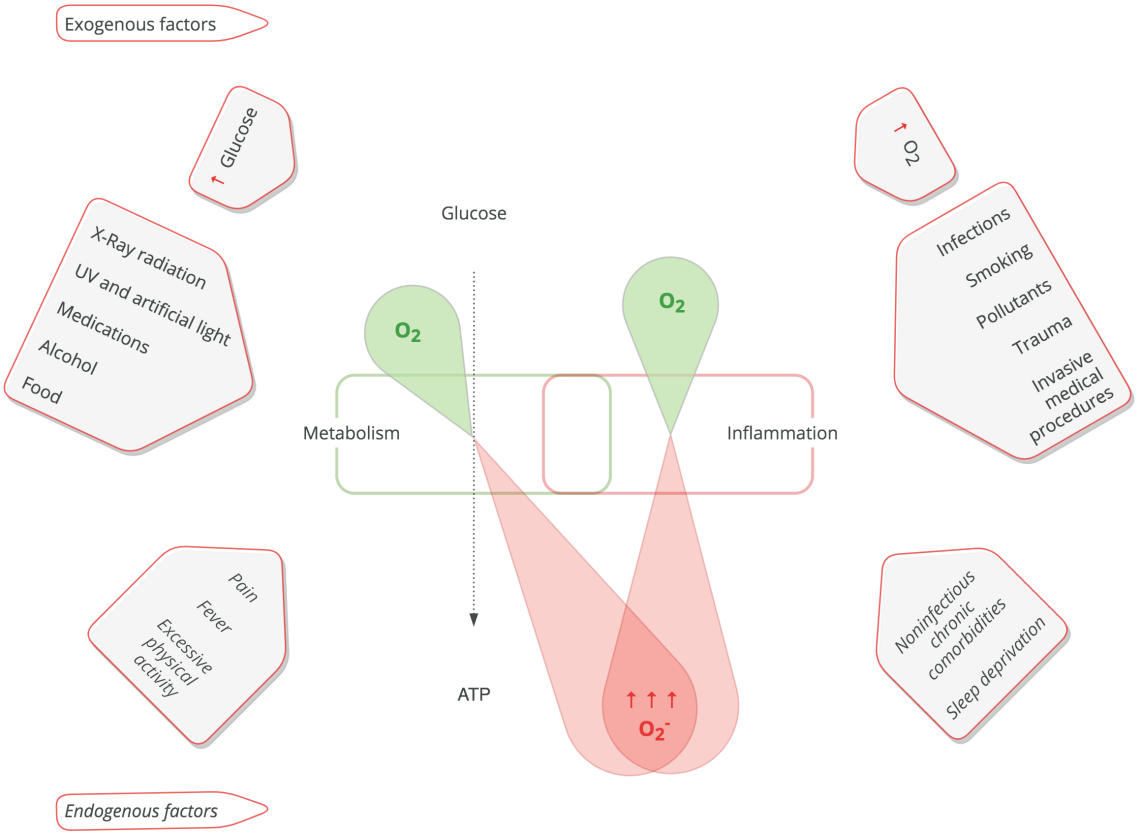

Fig. 2. Factors that increase oxidant production

A. Control of excessive oxidant production (Fig.2)

Factors that increase oxidant production:

1. Exogenous factors
   a) excessive glucose [11]
   b) excessive O2 [12]
   c) impairment of mitochondrial oxidative phosphorylation by X-Ray [13] and high dose of ultraviolet (UV), infrared (IR) and blue-violet light (screens), [14] ethanol, [15] certain medications and foods [16]
   d) triggering of inflammation by physical stresses [17]
2. Endogenous factors
   a) increased mitochondrial O2 consumption from pain [18], fever, [19] and excessive physical activity [20]
   b) sleep deprivation is accompanied by upregulation of inflammatory cytokine expression [21]
   c) triggering of inflammation by metabolites of chronic comorbidities such as obesity, [22] diabetes, [23] hypertension, [24] autoimmune diseases [25] and cancer. [26]

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Whether induced by exogenous or endogenous factors, inflammation is the most potent driver of oxidant production. [27]

Clinical applications: There are several ways to minimize the degree of oxidant production.

- Optimize management of chronic comorbidities.
- Avoid excessive O2 therapy; do not try to achieve the highest possible SpO2 level. [28]
- Avoid hyperglycemia and carbohydrate overfeeding.
- Increase intervals between meals. [29]
- Avoid certain foods such as fava beans, [30] chili pepper, [31] excessive fat [32] and meat. [33]
- Avoid ethanol and the use of other alcohols: the habitual use of alcohol-based hand sanitizers must be deliberately avoided. [34]
- Avoid certain medications such as NSAIDs, [35, 36] hydroxychloroquine [37] and chloroquine, [38] ivermectin, [39] dexamethasone misuse [40] and azithromycin. [41]
- Control fever primarily with physical methods. [42]
- Try to avoid mechanical ventilation unless there is an absolute need. [43]
- Avoid excessive exposure of eyes and skin to sun and artificial lights.
- Minimize exposure to X-Ray radiation by avoiding X-Rays if not absolutely necessary.
- Avoid active and passive smoking. [44]
- Avoid excessive physical activity.
- Mitigate pain primarily with physical methods. [45]

B. Neutralization of excessive oxidants (Fig.3)

Excessive oxidants are neutralized into nontoxic compounds by antioxidants that can be either exogenous, i.e. those that can be supplemented, or endogenous.

1. Exogenous antioxidants
   a) Ascorbic acid (Vit.C), an important water-soluble redox factor that can be synthesized by plants and animals with the notable exception of humans and other higher primates.
   b) Carotenoids, fat-soluble pigments in bright red, yellow and orange fruits and vegetables.
   c) Polyphenols, secondary metabolites of plants which contribute to their bitterness, astringency, color, flavor, odor and oxidative stability, e.g. flavonoids and coumarines.
   d) Vitamin E (Vit.E), a group of fat-soluble compounds found in vegetables and seeds.
   e) Glutathione (GSH), the major antioxidant, is synthesized by the body, and is also found in diet and supplements, both sources restoring its endogenous pool.

   During oxidant neutralization, exogenous antioxidants are converted to their oxidized form acting as oxidants. And the endogenous antioxidant, GSH, is required for recycling of these oxidized forms back to their antioxidant forms.[46] *Therefore, the antioxidant activity of exogenous supplements depends on the antioxidant activity of the endogenous pool.*

2. Endogenous antioxidants
   a) Superoxide dismutase (SOD) that is dependent on certain co-factors: Zn, Cu and Mn.
   b) Catalase that is dependent on Fe as a co-factor.
   c) Thioredoxin reductase that is dependent on Se as a co-factor.
   d) The GSH complex.

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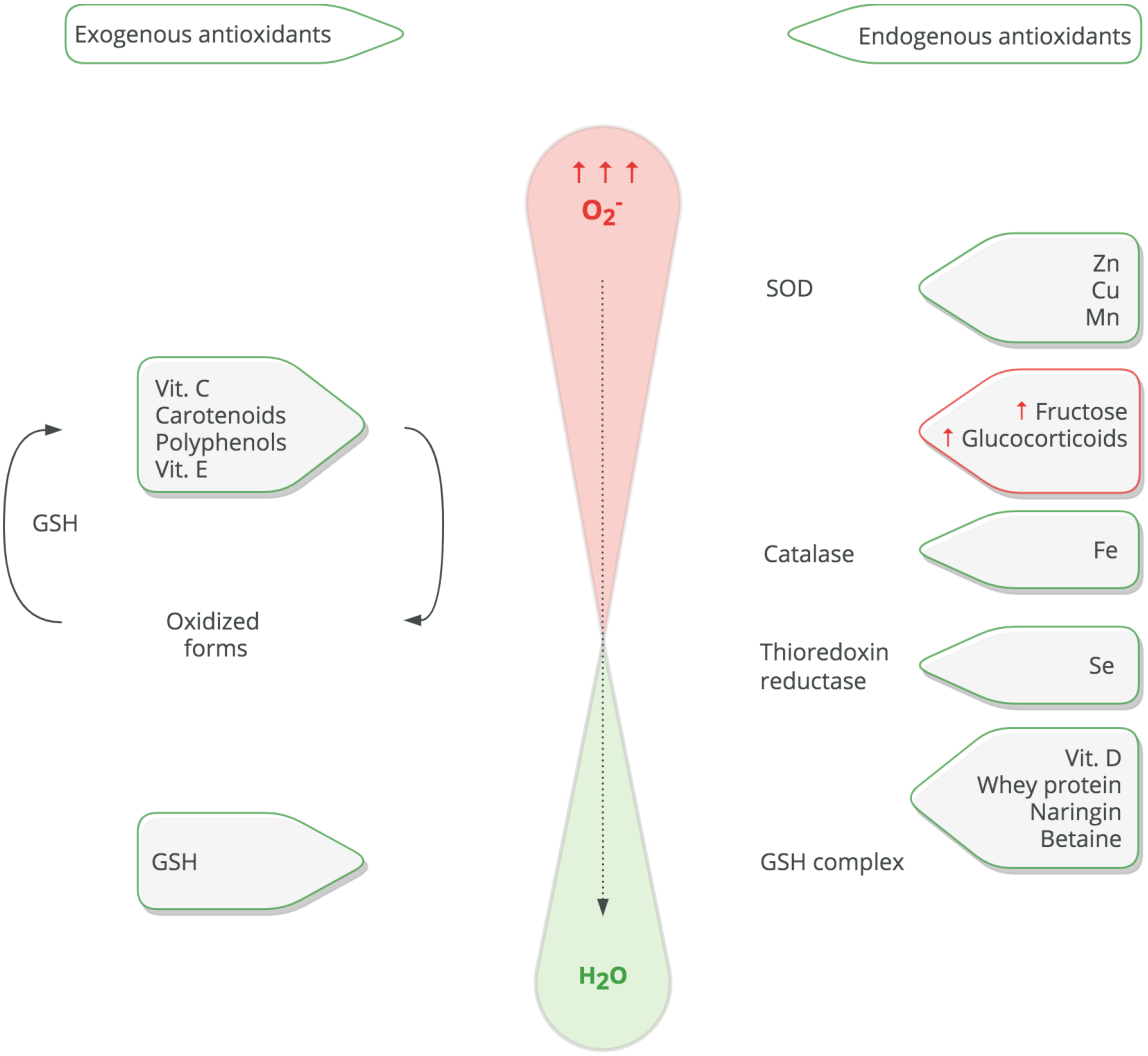

Fig. 3. Factors that affect oxidant neutralization

Factors that interfere with their function include congenital or acquired pathology of the AO system, e.g. G6PD deficiency, and certain supplements. For example, Vit. D, [47] naringin, [48] whey protein, [49] and betaine [50] induce gene expression and activity of endogenous antioxidants. In turn, glucocorticoids and fructose in high doses inhibit it. [50, 51]

The GSH complex (Fig.4) is the main component of the AO system. It is composed of GSH, glutathione peroxidase (GP), glutathione reductase (GR) and the oxidized form of GSH (GSSG). There are certain factors that affect the synthesis and recycling of GSH:

1. GSH synthesis
   a) GSH is synthesized from three amino acids: glutamate, cysteine and glycine.

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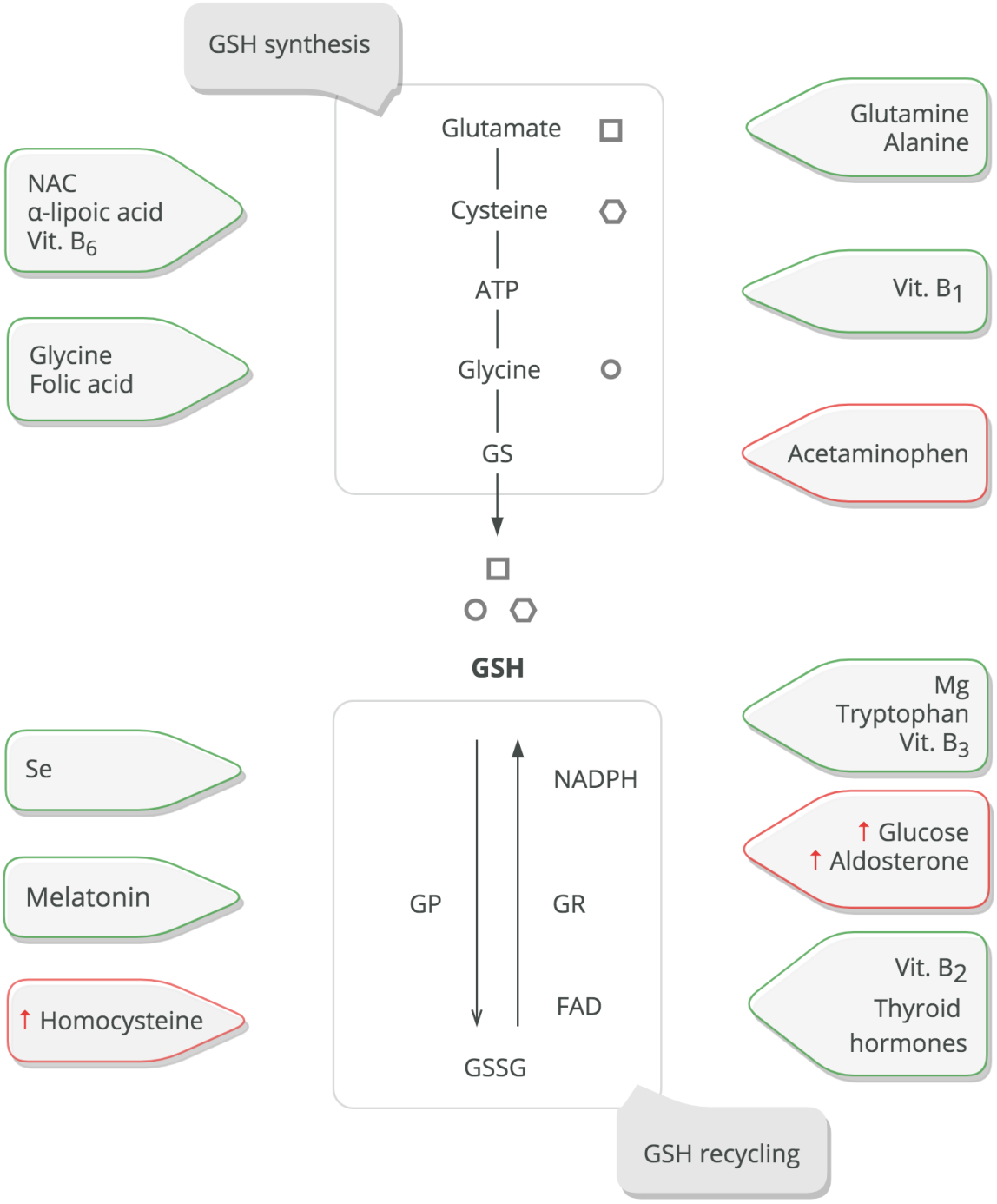

Fig. 4. Factors that affect GSH synthesis and recycling

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b) Glutamate is synthesized from alanine and glutamine which is decreased during inflammatory conditions. [52]
c) Cysteine synthesis requires vit. B6 (pyridoxine) as a co-factor and n-acetylcysteine (NAC) and α-lipoic acid as precursors. [53]
d) Glycine synthesis from serine requires folic acid. [54]
e) The GSH synthesis process is energy-dependent that requires ATP and vit. B1 (thiamine) is a co-factor that up-regulates metabolism for ATP production. [55]
f) Acetaminophen inhibits enzyme glutathione synthase (GS). [56]

2. GSH recycling
   a) During oxidant neutralization, GSH is oxidized to GSSG by GP that requires Se as a co-factor.
   b) Melatonin increases activity of GP. [57]
   c) Increased homocysteine levels inhibit GP and folic acid with vit. B12 are co-factors for homocysteine control. [58, 59]
   d) GR recycles GSSG back to GSH and is dependent on co-factors, NADPH and flavin adenine dinucleotide (FAD). [60]
   e) Vit. B3 (niacin) is a precursor and Mg is a co-factor for NADPH production. [61, 62]
   f) SARS-CoV-2 inhibits absorption of tryptophan, a precursor of niacin and melatonin, through ACE2 suppression in the small intestine. [63]
   g) Increased aldosterone levels decrease G6PD level. [64]
   h) Hyperglycemia aggravates insulin resistance increasing G6PD deficit. [65]
   i) Thyroid hormones and vit. B2 (riboflavin) are co-factors for FAD production. [66]

Clinical applications: There are a number of ways to increase the neutralization of excessive oxidants.

1. Several antioxidants, co-factors and precursors can be supplied exogenously by diet and/or supplements:
   - Plants and mushrooms are natural sources of exogenous antioxidants, dose of which matters. In small doses, they work as antioxidants and, in high doses, they can overload the regenerative capacity of endogenous antioxidants and work as oxidants. [67] In addition, anti-nutrients such as fructose have dose-dependent effects as well.
   - Ascorbic acid can be administered IV in critically ill patients. [68]
   - Microelements: Zn, Cu, Mn, Fe, Se and Mg supplied in sufficient amounts. [69]
   - Vit. B1 (thiamine) can be administered IV in critically ill patients. [70]
   - Vit. D, B6 (pyridoxine), B2 (riboflavin), B12 (cyanocobalamin), folic acid, α-lipoic acid and amino acids supplied in sufficient amounts. [71]
   - NAC and glutathione (GSH) can be administered orally, IV or nebulized. [72, 73]
   - Vit. B3 (niacin) supplements administered during convalescence to support the AO system. [74, 75]
2. Avoid chronic use and high doses of glucocorticoids.
3. Avoid acetaminophen. [76]
4. Tight control of thyroid hormones. [77]
5. Tight control of blood glucose levels. [78]
6. Optimize management of chronic comorbidities.

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C. Upregulation of NO production (Fig.5)

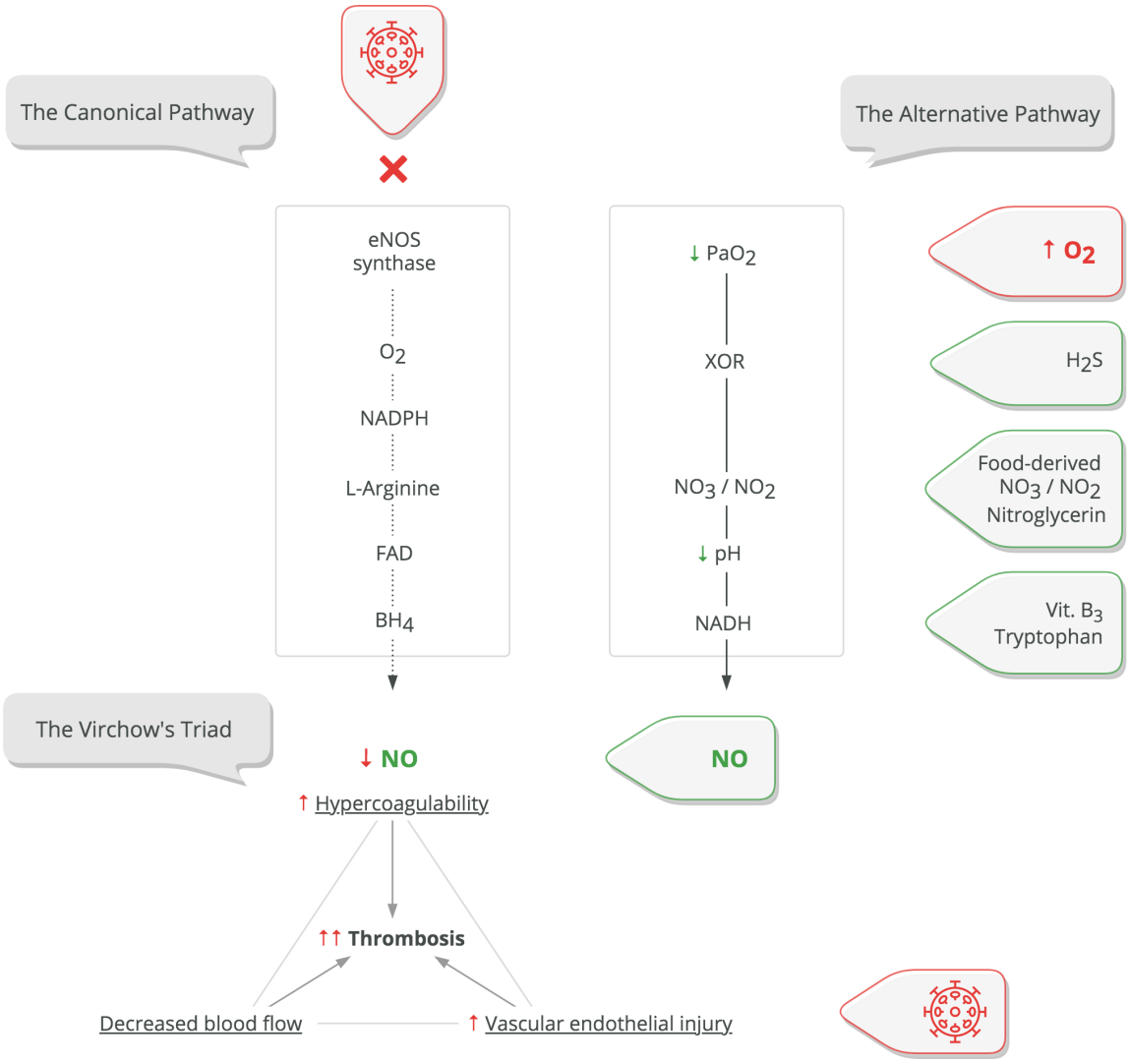

Fig. 5. Factors that affect NO production and the Virchow's Triad

Physiologically, vascular NO has three main roles:

1. As a vasodilatator, it maintains relaxation of blood vessels.
2. As an antioxidant, it inhibits NADPH oxidase, as depicted in Fig.1.
3. As an anticoagulant, as depicted in Fig. 5, NO affects *the Virchow's Triad* of thrombosis.

As mentioned above, SARS-CoV-2 suppresses NO production increasing hypercoagulability. Moreover, common to other pathogens, SARS-CoV-2 injures vascular endothelial cells. These processes

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predispose to thrombosis which is a major clinical complication of COVID-19. [79]
Additionally, as an antiviral, NO suppresses SARS-CoV-2 replication through inhibition of protease activity. [80]

Under normal conditions, vascular NO is produced in two ways, by: [81]

1. *The Canonical pathway*, through eNOS synthase. It requires tetrahydrobiopterin (BH4) that is a derivative of folic acid, arginine, O2, NADPH and FAD. [82] It is inhibited by SARS-CoV-2.
2. *The Alternative pathway*, through reductase activity of xanthine oxidoreductase (XOR). It requires nitrates/nitrites (NO3/NO2), the reduced form of nicotinamide adenine dinucleotide (NADH) and is potentiated by acidosis (↓pH) and hypoxemia (↓PaO2). [83] XOR is activated by sulfur compounds such as hydrogen sulfide (H2S). [84]

Importantly, COVID-19-induced oxidative stress can increase the levels of methemoglobin which makes SpO2 calculation inaccurate. [85] It falsely causes a low SpO2 by pulse oximetry in patients with a normal PaO2. [86] This can be misleading and can result in an unnecessary administration of O2 and suppression of the rescuing XOR pathway. [87]

Clinical applications: The goal is to reduce *the Virchow's Triad* to prevent thrombosis by:

1. Restoring NO to *decrease hypercoagulability*. NO can be supplied exogenously and/or produced through the alternative pathway:
   - Boost NO3/NO2 which can be supplied by diet, e.g. beetroot and spinach, [88] and through supplements, e.g. nitroglycerin. [89]
   - Avoid excessive O2 therapy; do not try to achieve the highest possible SpO2 level.
   - Do not correct acidosis unless it is severe or associated with cardiovascular compromise.
   - Boost tryptophan and vit. B3, as precursors of NADH.
   - Boost sulfur compounds which can be supplied by a diet rich in allium vegetables such as garlic and onions. [90]
2. *Maintaining blood flow* through:
   - Avoiding increases in blood viscosity with adequate hydration based on urine output. [91]
   - Promotion of blood circulation by active and passive movements. [92]
   - Supporting ventilation and perfusion of all West's lung zones by breathing exercises and prone positioning. [93, 94]
3. Controlling the degree of oxidative stress to *decrease vascular endothelial injury* through therapeutic interventions that minimize oxidant production and induce its neutralization.

Conclusion

In order to mitigate the excessive immune response and not to aggravate it, key pathobiochemical points of COVID-19 pathogenesis enable to apply the essential minimum: the dose makes the poison, *Dosis sola facit venenum.*

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