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(A review article)

The potential effects of antioxidants as adjuvants to current therapeutics of COVID-19 pandemic: lessons from disease pathophysiology

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Abstract: The COVID-19 pandemic is still challenging. Antioxidants are missing vital remedies in COVID-19 treatment. Oxidants are increased and antioxidants are decreased in COVID-19 patients which may affect the disease severity. This review investigates that and provides practical preventive and therapeutic solutions. Error-prone RNA polymerases explain SARS-CoV-2 mutagenesis and the emergence of novel strains. COVID-19 pathogenesis starts with the attachment of spike proteins to angiotensin-converting enzyme-2 receptors on target cells in the respiratory and digestive systems. SARS-CoV-2 induces oxidative stress-induced acute inflammatory processes. Neutrophilic degranulation releases IL-6 and TNF-α. This enhances oxidative stress and cytokine storm-induced acute respiratory distress syndrome with overwhelming proinflammatory hypercytokinemia, multisystem tissue damage, respiratory failure, and shock. COVID-19 mortality rates differ globally, with Saudi Arabia among the countries having the lowest fatalities. COVID-19 patients COVID-19 exhibited depleted total antioxidant capacity that can be regarded as a predictive marker of severity. COVID-19 patients had elevated levels of oxidative stress and reduction of antioxidant markers. Gastrointestinal symptoms of the COVID-19 pandemic usually worsen with disease progression and include anorexia, diarrhea, liver injury, nausea, and abdominal pain. Antioxidants (e.g. glutathione) deficiency aggravated SARS-CoV-2 infection. High serum-reduced glutathione causes decreased ROS and a shorter course of illness. Antioxidants are strongly suggested as adjuvant therapeutics to combat the pandemic. We previously reported promising TaibUVID antioxidants that help COVID-19 patients to recover. Antioxidant (e.g. glutathione) deficiency exaggerates SARS-CoV-2 infection. Glutathione intake results in decreased ROS and shortened illness course. Pneumonia, dysgeusia, and hyposmia improved immediately upon antioxidant treatment. All TaibUVID components raise glutathione levels, enhance immunity, combat viruses, and exert tissue protection. This review discusses this vital issue.

Keywords: COVID-19, pathophysiology, cytokine storm, antioxidants, glutathione, TaibUVID

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بحث مرجعي

الآثار المحتملة لمضادات الأكسدة كمواد مساعدة للعلاجات الحالية لوباء COVID-19:دروس من الفسيولوجيا المرضية للأمراض

معتصم صالح أبوعنق

(قدم للنشر في 1444/9/6هـ؛ وقبل للنشر في 1445/2/14هـ)

مستخلص البحث: لا تزال جائحة COVID-19 تمثل تحديًا. و تعتبرمضادات الأكسدة من العلاجات الحيوية في علاج COVID-19. و تزداد المواد المؤكسدة بينما تنخفض مضادات الأكسدة لدى مرضى كوفيد -19 مما قد يؤثر على شدة المرض. تبحث هذه المراجعة في ذلك وتثبت الحلول الوقائية والعلاجية العملية. و تسهل بوليمرات الحمض النووي الريبي المعرضة للخطأ حدوث طفرات فيروس السارس-CoV-2 وظهور سلالات جديدة. و يبدأ التسبب في الإصابة بفيروس COVID-19 بربط بروتينات سبايك بمستقبلات الإنزيم -2 المحول للأنجيوتنسين على الخلايا المستهدفة في الجهاز التنفسي والجهاز الهضمي. و يساعد فيروس السارس- CoV-2 حدوث العمليات الالتهابية الحادة التي يسببها الإجهاد التأكسدي مثل المواد الالتهابية انترلوكين-6 (IL-6) وعامل تنكرز الأورام ألفا TNF-α. كما يعزز الإجهاد التأكسدي ومتلازمة الضائقة التنفسية الحادة التي تسببها عاصفة السيتوكينات من تلف الأنسجة متعدد الأنظمة، وفشل الجهاز التنفسي والصدمة الدموية. و تتفاوت معدلات وفيات COVID-19 على مستوى العالم ، حيث سجلت المملكة العربية السعودية أدنى معدلات الوفيات. كما أظهر مرضى COVID-19وباء كورونا نقصا في القدرة الكلية لمضادات الأكسدة الكاملة والتي يمكن اعتبارها علامة تنبؤية لشدة المرض. و لقد كان لدى مرضى COVID-19 مستويات مرتفعة من الإجهاد التأكسدي يصحبه نقص في علامات مضادات الأكسدة. و عادة ما تتفاقم أعراض الجهاز الهضمي لوباء COVID-19 مع تطور المرض وتشمل فقدان الشهية والإسهال وإصابة الكبد والغثيان وآلام البطن. كما أدى نقص مضادات الأكسدة (مثل الجلوتاثيون) إلى تفاقم عدوى السارس- CoV-2. و يؤدي انخفاض مستوى الجلوتاثيون في الدم إلى انخفاض نسبة الأكسجين إلى الدم وقصر فترة المرض. و يُقترح بشدة استخدام مضادات الأكسدة كعلاجات مساعدة لمكافحة الوباء. لقد أثبتنا سابقًا أن مضادات الأكسدة الواعدة TaibUVID ساعدت مرضى COVID-19 على التعافي. و يؤدي نقص مضادات الأكسدة (مثل الجلوتاثيون) إلى تضخيم عدوى السارس. كما أدت نتائج تناول الجلوتاثيون إلى تقليل أنواع الأكسجين التفاعلية و نقص مسار المرض مع تحسن الالتهاب الرئوي وعسر الهضم ونقص حاسة الشم فور العلاج بمضادات الأكسدة. و تعمل جميع مكونات TaibUVID على رفع مستويات الجلوتاثيون وتقوية المناعة ومكافحة الفيروسات و حماية الأنسجة كما نناقشه هنا.

كلمات مفتاحية: كوفيد-19 ، الفسيولوجيا المرضية، عاصفة السيتوكينز، مضادات الاكسدة، الجلوتاثيون، TaibUVID .

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1. INTRODUCTION

Antioxidants are still missing vital remedies in COVID-19 treatment that need more light to be shed on them for more effective therapeutic outcomes. Our previous publications confirm the merits of antioxidants in combating the COVID-19 pandemic, particularly at the early stages of disease pathophysiology. Oxidants are increased and antioxidants are decreased in COVID-19 patients which may affect its severity. This review investigates that and provides practical preventive and therapeutic solutions.

SARS-CoV-2 is the causative virus of the COVID-19 pandemic. This virus belongs to the beta-coronaviruses family that are also implicated in the pathogenesis of severe acute respiratory syndrome (SARS) and the subsequent Middle East respiratory syndrome (Patel, Patel, Vunnam, Hewlett, Jain, Jing & Vunnam (2020). The COVID-19 pandemic first emerged in December 2019 in the Far East where many patients presented with atypical pneumonia that was first observed in health centers in Wuhan, China. Oxidant/antioxidant status is impaired in COVID-19 patients due to depleted total antioxidant capacity that can be regarded as a predictive marker of COVID-19 severity (Wang, Horby, Hayden & Gao 2020b). On March 11, 2020, the WHO declared COVID-19 as a worldwide pandemic. Interestingly, the serum levels of reduced glutathione, total antioxidant capacity, and total oxidant status were estimated in COVID-19 patients. It was found that COVID-19 patients had elevated levels of oxidative stress and reduction of antioxidant indices that aggravated the severity of COVID-19 in hospitalized patients. Moreover, that strongly suggested antioxidants as adjuvant therapeutics to combat the pandemic (Mann, Sekhon & Sekhon 2021). Patients presented with vague pneumonia. Early health reports indicated that these cases had bird flu, swine flu, and influenza-like symptoms. SARS-CoV-2 is genetically similar to SARS-CoV-1 (by about 79-80%) and to MERS-CoV (by about 51.8%) and is also 96% similar to the whole genomic structure of coronavirus-affecting bats (Chen, Liu, & Guo 2020). This novel virus massively disseminated across the world within a relatively short period (a few months), resulting in an emerging pandemic that threatened millions of lives and constituted a real danger to human health worldwide. Later, the causative virus was delineated to be a novel SARS-CoV-2 that maximally and rapidly caused worldwide morbidity and mortality in a relatively short duration. Despite worldwide lockdown, SARS-CoV-2 caused a lethal pandemic threatening human health (Rothan and Byrareddy 2020). The current COVID-19 pandemic has caused 3.7 million victims and more deaths are expected in the coming months (Arias-Carrasco, Giddaluru, Cardozo, Martins, Maracaja-Coutinho & Nakaya 2021). Gastrointestinal presentation is a serious topic related to COVID-19 lethality. In this review article, the merits of antioxidants for treating COVID-19 are introduced and correlated to pandemic pathology and pathophysiology, and new vital therapeutic targets are discussed with a special emphasis on the gastrointestinal picture.

Genome of SARS-CoV-2

SARS-CoV-2 belongs to the coronaviruses, i.e. it is an enveloped virus having a single-stranded nucleic acid (positive-sense RNA) lacking genomic segmentation. The viral genome (~30 kb in size) carries genetic information for synthesizing about 16 non-structural proteins (which facilitate viral replication, entry, and pathogenesis). These structural proteins include the envelope protein (E), membrane protein (M), nucleocapsid protein (N), and spike glycoprotein (S) (Kim, Lee, Yang, Kim, Kim & Chang 2020). The genomic sequence of SARS-CoV-2 confirms that it is about 75-80% similar to the genomic structure of SARS-CoV (Andersen, Rambaut, Lipkin, Holmes & Garry 2020). There are two major subtypes of SARS-CoV-2 upon studying 103 SARS-CoV-2 genomes (referred to as L and S) using single nucleotide polymorphisms (Tang, Wu, Li, Song, Yao, Wu, Duan, Zhang, Wang & Qian 2020b).

Future mutagenesis of SARS-COV-2 viruses may occur as they have error-prone RNA-dependent RNA polymerases. This may increase the frequency of future genetic mutations, making

subsequent genomic recombination possibilities quite common (Kautz and Forrester 2018; Smith 2017). This may explain the evolution of SARS-CoV-2. In Wuhan, China, the L type of SARS-COV-2 was seen in about 70% of COVID-19 patients and was confirmed to be more pathogenic and infectious compared to the original S type (Tang et al. 2020b).

COVID-19 transmission

The SARS-CoV-2 virus remains contagious in air droplets for approximately 3 hours (median half-life of 1.1-1.2 hours). Moreover, SARS-CoV-2 remains on plastic surfaces and stainless steel objects for an average period of three days (72 hours) after virus contamination. Moreover, the SARS-CoV-2 virus has been found on copper or metal surfaces for 4 to 24 hours. Aerosol and fomite transmission is highly likely as the virus remains infectious in aerosols for three hours and on contaminated surfaces for more than 72 hours (Van Doremalen, Bushmaker, Morris, Holbrook, Gamble, Williamson, et al., 2020).

SARS-CoV-2 infection has a high mortality rate that increases with age. In the 55- to 74-year-old age group, the mortality rate is 1.4-4.9%; this increases to 4.3-10.5% in the age group 75-84 years. However, the highest fatality rate is 10.4-27.3% in the age group above 85 years (Uddin, Mustafa, Rizvi, Loney, Al Suwaidi, Al-Marzouqi, et al., 2020).

SARS-CoV-2 entry into target cells

SARS-CoV-2 synthesizes many non-structural proteins that negatively impair the host's immune system and host cell physiological functions by enhancing virus virulence factors. A close interaction occurs between the SARS-CoV-2 virus and host cell receptors to mediate virus entry. In many people, the COVID-19 pandemic remains symptomless, while in other patients the pandemic may present with severe complications, e.g. pneumonia, respiratory distress, and respiratory failure (Astuti 2020).

Enveloped viral species, e.g. Coronaviridae target angiotensin-converting enzyme (ACE) cellular receptors that mediate virus internalization via endocytosis resulting in endosome formation. That endosome is acidic and this acidity continuously and progressively increases. Protonation of the binding viral glycoproteins soon increases. Enzyme activities are enhanced, facilitating the binding of viral proteins to the virus membranes and other cellular membranes, with the final release of the viral RNA into the cytoplasm. Upon coronavirus attachment to cellular membranes, viral spike protein interacts with cellular receptors followed by acid-dependent proteolytic cleavage of the viral spike proteins using a protease enzyme (cathepsin). This is followed by the fusion of viral and cellular membranes to form endosomes. The acidic pH of endosomes accelerates the viral-cell fusion processes (Tang, Bidon, Jaimes, Whittaker & Daniel 2020a).

Remedies used to treat COVID-19 patients e.g. Remdesivir, Ivermectin, and hydroxychloroquine can bind the active position viral protease protein (Hoffmann, Kleine-Weber, Schroeder, Krüger, Herrler, Erichsen, et al., 2020). The emergence of a new UK variant B.1.1.7 of SARS-CoV2 virus had exaggerated COVID-2 suffering. SARS-CoV2 virus is mainly transmitted through coughs, sneezes, talks, or breaths and on different surfaces (Mohapatra, Das, Pintilie & Dhama 2021). With the emergence of the new variants of concern of SARS-CoV-2, the efficacy of vaccines requires consideration. Vaccines' lack of efficacy against variants of concern of SARS-CoV-2 may subject the vaccinated population to health threats. Students in countries with the highest rates of infection (e.g., India, the USA, and Brazil) are prone to infection. SARS-CoV-2 strain variant (UK variant B.1.1.7) had spread in various Indian states among students. This maximizes vaccination necessity (Hoffmann et al. 2020; Mohapatra et al., 2021; Sah, Khatiwada, Shrestha, Bhuvan, Tiwari, Mohapatra, et al., 2021; & Sungnak, Huang, Bécavin, Berg, Queen, Litvinukova, et al., 2020)).

Pathophysiology of COVID-19

SARS-CoV-2 is a single-stranded RNA virus containing four different viral proteins. The spike proteins attach SARS-CoV-2 to ACE2 and ease viral entry to target host cells. The spike protein of

SARS-CoV-2 is vital for receptor specificity, tissue homing, and cellular binding. ACE2 expression is present in the oral mucosa and nasal epithelial cells of the upper respiratory system and explains the high transmission rates of the virus (Sungnak et al. 2020).

ACE2 receptors are found in type 2 alveolar cells and muscle cells of the pulmonary vasculature. This partially gives explanations about the severe respiratory symptomatology associated with these viruses (Tang et al. 2020a). Male patients suffer more from inflammatory disease than females. Hormones may play a role. Females may be more protected from respiratory viral pathogens of SARS-CoV-2, than males possibly due to the effects of estrogen and other sex hormones on both T and B lymphocytes (Vadakedath, Kandi, Mohapatra, Pinnelli, Yegurla, Shahapur, et al., 2021).

ACE2 receptors are also found in the epithelial cells all over the gastrointestinal tract, e.g. oral mucosa, cytoplasm of the gastric and intestinal epithelia and the ciliary lining of the digestive glands, colonic enterocytes, myocardial cells, vascular endothelium, proximal tubule, bladder urothelial cells, and cholangiocytes (Xiao, Tang, Zheng, Liu, Li & Shan 2020). In a recent study, the *ACE2* gene was found to exhibit single nucleotide polymorphisms with many different allele frequencies across the globe (Cao, Li, Feng, Wan, Huang, Sun, et al., 2020). SARS-CoV-2 may direct damage to the intestinal mucosa. This can lead to increased intestinal permeability to foreign pathogens by compromising intestinal barrier function, resulting in diarrhea and malabsorption (Gu, Han & Wang 2020).

The allele frequency of the host gene varies among males and females. In COVID-19 patients, many risk factors aggravate infection (Table 1). The presence of viral nucleocapsid protein was confirmed in the gastrointestinal lumen of many digestive organs, e.g. stomach, duodenum, and rectum glandular epithelial cells excluding the esophagus. The SARS-CoV-2 virus subverts cellular capabilities to serve the viral replication process. Viral RNA polymerase is quite necessary for viral replication (Xu, Chen, Wang, Feng, Zhou, Li, et al., 2020). The incubation period for SARS-CoV-2 may last 4-14 days. Within this period, symptomatology may appear and is mostly mild (80%). However, severe cases may be encountered (20%) when comorbidities and high viral load are present (Wang, Tang and Wei 2020c). Severe symptomatology encountered with novel SARS-CoV-2 results from the interaction of immune responses, cytokines effects, and defensive measures.

Cytokine storm

The cytokine storm takes place as a consequence of events in response to the pathogenesis of SARS-CoV-2 infection. This causes an increase in the volume of mucus and fluids inside the lung alveoli, with subsequent collapse of pulmonary function, up to respiratory failure (Corman, Landt, Kaiser, Molenkamp, Meijer, Chu, et al., 2020).

Table 1 : Risk factors aggravating novel SARS-CoV-2 infection (Zhou, Yu, Du, Fan, Liu, Liu, et al., 2020; Lippi, Wong & Henry 2020; Baud, Qi & Nielsen-Saines 2020; Verma and Shakya 2021)

- **Age:** older than 60 years of age
- **Co-morbidities** (particularly chronic diseases): diabetes mellitus, diabetic complications, chronic renal disease, hypertension, hyperlipidemia, cardiovascular diseases, cancer
- **Differential expression of the ACE2 receptor**
- **Chronic obstructive pulmonary disease**
- **Malnutrition**
- **Immunocompromise**
- **Viral load**
- **Occupation** (physicians, physician's families, and hospital staff)
- **Virulence** of COVID-19 strains and genomic mutations

Step 1: SARS-COV-2 infects the upper respiratory tract

In the early stages of COVID-19, coronavirus infection starts with the inhalation of droplets containing SARS-CoV-2 virions that gain access to the nasal mucosa, causing cellular swelling and inflammation. Respiratory epithelial cells (having cilia) and mucus (a product of goblet cells of the respiratory tract) extrude the pathogen via mucociliary defense mechanisms. Co-morbidities such as diabetes, cardiovascular disease, or tobacco use impair pathogen excretion via this innate mechanism, which allows for virus colonization in the lower respiratory tract (Brodin 2021). Patients infected with COVID-19 are usually asymptomatic in cases where there is no colonization of the lower respiratory tract. Host barriers and defenses of the respiratory epithelial lining, e.g. immunoglobulin A, reduced glutathione, and beta-defensins tend to clear COVID-19 infection in its early stages, although patient nasopharyngeal PCR swabs are still positive (Cao and Li 2020). When SARS-CoV-2 arrives at the lower respiratory tract, it attaches to ACE2 on type II alveolar pneumocytes (which produce surfactant and regenerate type I alveolar pneumocytes that facilitate gas exchange) via the viral S protein. Subsequently, SARS-CoV-2 enters target cells, releases its single-stranded RNA genome, and utilizes the host enzyme machinery for viral replication. Consequently, damaged type II pneumocytes result in decreased surfactant levels, and suppressed type I pneumocytes functions impair gas exchange and minimize lung compliance, leading to lung edema and pneumonitis (Mason 2020). Intestinal epithelial cells have ACE2 receptors, allowing SARS-CoV-2 to infect intestinal cells (enterocytes), causing early gastrointestinal manifestations, e.g. diarrhea (Guan, Ni, Hu, Liang, Ou, He, et al., 2020). Based on that, COVID-19 patients may present with respiratory or gastrointestinal symptoms (Table 2).

Step 2: SARS-CoV-2 induces the oxidative stress-induced acute inflammatory process

Local immunological defenses in pulmonary tissues affect type II pneumocytes, alveolar macrophages, and dendritic cells. Macrophages and type II pneumocytes secrete IL-8 (a vital neutrophil chemotactic agent) (Costela-Ruiz, Illescas-Montes, Puerta-Puerta, Ruiz & Melguizo-Rodríguez 2020). Acute inflammation occurs with neutrophil and monocyte migration to lung alveoli (García 2020), with neutrophilic degranulation and release of acute phase reactants, e.g. IL-6 and TNF-α. Phagocytes use reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a coenzyme for NADPH oxidase for generating cytotoxic reactive oxygen species, i.e. hypochlorite and hydrogen peroxide (Polonikov 2020). Acute inflammatory processes caused by a combination of ROS and pro-inflammatory cytokines participate in causing the severe parenchymal lung injury commonly encountered in COVID-19. Decreased levels of pro-inflammatory cytokines, reactive oxygen species, hypochlorite, and hydrogen peroxide are associated with rapid recovery and a mild course of COVID-19 illness (Polonikov 2020).

Both components of type I interferon (IFN-α and IFN-β) play a significant role in the innate response to viruses. Human embryonic kidney (HEK293) cells expressing structural proteins of SARS-CoV-2 maximally resisted the effects of IFN-β and NF-κβ (Li, Liao, Wang, Tan, Luo, Qiu et al., 2020a). Moreover, incubating Vero cells with recombinant human IFN-α caused decreased SARS-CoV-2 viral titers compared to non-incubated Vero cells (Tang et al. 2020a).

Cytotoxic T lymphocytes recognize viral antigens presented by antigen-presenting cells (e.g. dendritic cells and B cells) in association with major histocompatibility complex (MHC) Class I. Cytotoxic T lymphocytes degranulate, causing released cytotoxic perforins and granzyme-B. Perforin proteins cause perforations and increase the permeability of the membranes of virus-infected cells, while granzymes cause proteolytic activation of intracellular caspases, resulting in apoptosis (Tang et al. 2020a). Uncontrolled and dysregulated secretion of inflammatory and pro-inflammatory cytokines (as TNF-α, IL-1, and IL-6 causing cytokine storm) positively correlates with viral infection severity and high mortality rate via recruiting macrophages, T and B cells in the lung alveolar cells (Mantlo, Bukreyeva, Maruyama,

Paessler & Huang 2020). Hypercytokinemia causes acute respiratory distress syndrome and multiple organ damage. Immunological response against SARS-CoV-2 is related to race, gender, and age. Many therapeutic strategies investigate the cytokine storm in patients with severe COVID-19 (Rabaan, Al-Ahmed, Muhammad, Khan, Sule, Tirupathi, et al., 2021b).

Upon antigen presentation (e.g. due to SARS-CoV-2 infection), T helper lymphocytes (Th1 and Th2 subtypes) release inflammation-induced cytokines as IL-6, interferon-gamma (IFN-γ), IL-4, granulocyte-macrophage colony-stimulating factor, IL-2, and IL-10. IL-2 enhances the maturation of helper and cytotoxic T cells, while IL-4 enhances B cell growth and differentiation into plasma cells (to secrete antibodies) (figures 1-2) (Rabaan, Al-Ahmed, Garout, Al-Qaaneh, Sule, Tirupathi, et al., 2021a). IFN-γ enhances phagocytosis (exerted by macrophages and monocytes) and potentiates natural killer (NK) cells-induced lysis of virus-infected cells (Lang, Lee, Teijaro, Becher & Hamilton (2020). The granulocyte-macrophage colony-stimulating factor is a glycoprotein that induces maturation and then differentiation of neutrophils and CD14+/CD16+ monocytes, which produce massive amounts of IL-6 that are not seen in healthy subjects (Figure 1) (Boyette, Macedo, Hadi, Elinoff, Walters, Ramaswami, et al., 2017). Immune cells, e.g. activated lymphocytes, macrophages, and neutrophils produce different inflammatory cytokines such as IL-6 and TNF-α. IL-6 induces fever and increases the production of acute-phase proteins. TNF-α enhances leukocyte-induced development of disseminated intravascular coagulopathy and septic shock (Figure1) (Velazquez-Salinas, Verdugo-Rodriguez, Rodriguez & Borca 2019). Increased serum ferritin (> 400 ng/ml) was reported to be high in patients having severe COVID-19 disease upon hospitalization. Serum ferritin levels were 3 and 4 times higher in patients who died than those observed in patients who survived (Gómez-Pastora, Weigand, Kim, Wu, Strayer, Palmer, et al., 2020). High serum ferritin and IL-6 are both diagnostic and prognostic markers of COVID-19 deterioration, progression, and deterioration of the cytokines storm. Patients who recovered tended to have lower serum IL-6 and ferritin levels (Liu, Zhang, Yang, Ma, Li, Zhang, et al., 2020). The cytokine storm (with increased levels of IL-6) results in increased ferritin and hepcidin levels. This indirectly causes lethal oxidative stress via sequestering iron intracellularly with the resultant generation of reactive nitrogen species, reactive oxygen species, and reactive sulfur species. That collectively maximizes tissue damage in affected organs, e.g. the gastrointestinal tract, respiratory tract, and elsewhere (Cortese-Krott, Koning, Kuhnle, Nagy, Bianco, Pasch, et al., 2017). Sequestered iron may react with clotting factors in coagulation pathways, resulting in hypercoagulable conditions (Tang, Zhang, Fang, Han, Wang, Wang, et al., 2020c). Moreover, high levels of intracellular iron can enhance a recently reported cell death mechanism termed ferroptosis (Gao, Monian, Pan, Zhang, Xiang & Jiang 2016).

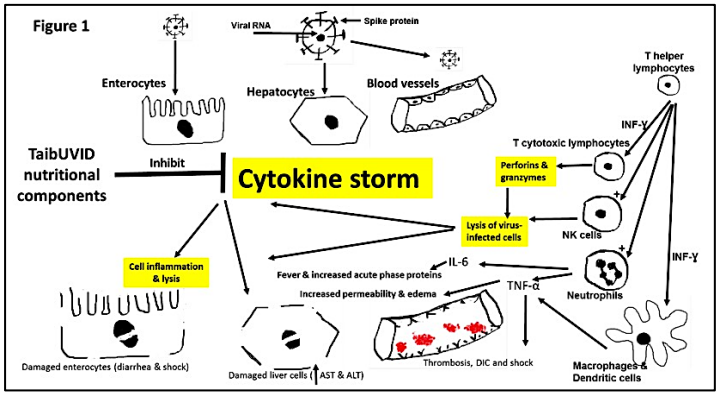

Figure 1. Pathophysiology of cytokine storm-induced death in COVID-19 patients

Figures legends

Figure 1. Pathophysiology of cytokine storm-induced death in COVID-19 patients: SARS-CoV-2 virus infects respiratory as gastrointestinal cells e.g. enterocytes and hepatocytes. SARS-CoV-2 also afflicts vascular endothelial cells. Routes of entry in all are ACE-2 receptors. Immunological responses include the activation of T helper lymphocytes (immunological orchestrator) that activate T cytotoxic, macrophages, neutrophils, and NK cells. Subsequent cytokines production participates in cell damage and hypercytokinemic-induced death. T cytotoxic cells produce perforins and granzymes that cause damage to virus-infected cells. NK cells cause lysis of virus-infected cells. Neutrophils degranulate causing the release of interleukin-6 causing fever and increased acute phase proteins. Both neutrophils and macrophages produce tumor necrosis factor-α that enhances vascular permeability, vascular thrombosis, edema, DIC, and septic shock. That collectively causes cellular damage to enterocytes (diarrhea and shock) and hepatocytes (raised serum liver enzymes, ALT, and AST). TaibUVID nutritional components (nigella sativa, natural honey, costus, senna, fennel, and chamomile) suppress inflammatory cytokines production and effects and were reported to effectively help cure COVID-19 patients.

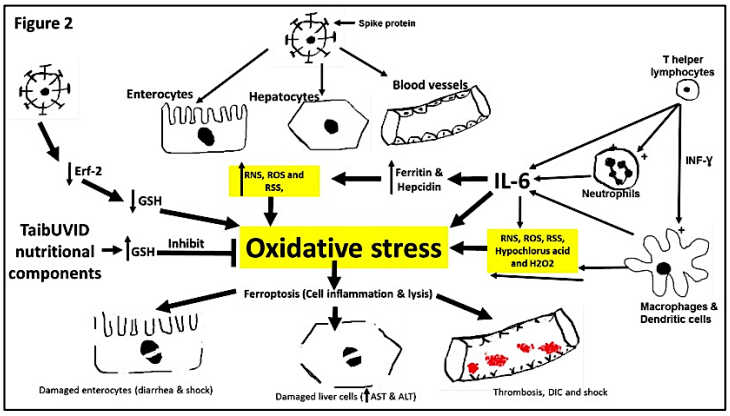

Figure 2. Pathophysiology of oxidative stress-induced death in COVID-19 patients:

Figure 2. Pathophysiology of oxidative stress-induced death in COVID-19 patients: Oxidative stress is a key player in cell damage and cell death in COVID-19 patients. Immunological responses include activation of T helper lymphocytes (immunological orchestrator) that activate T cytotoxic, macrophages and neutrophils. T helper lymphocytes, neutrophils, and macrophages produce interleukin-6 that enhances serum ferritin and hepcidin causing increased RNS, ROS, and RSS. Concomitantly, SARS-CoV-2 causes decreased Erf-2 which decreases serum GSH. All that increases oxidative stress vs. antioxidant power causing cell damage and apoptosis (ferroptosis). That collectively causes cellular damage to enterocytes (diarrhea and shock) and hepatocytes (raised serum liver enzymes, ALT, and AST). TaibUVID nutritional components (nigella sativa, natural honey, costus, senna, fennel, and chamomile) cause increased glutathione and decreased oxidative stress. Such effects effectively help cure COVID-19 patients. GSH reduced glutathione. Erf-2, erythroid releasing factor-2, RNS, reactive nitrogen species, ROS, reactive oxygen species, RSS, reactive sulfur species

Step 3: Either recovery or progression Recovery

As previously reported by the center for disease control, COVID-19 resolution involves recovery from the fever and respiratory symptoms with no

use of drugs (Wang, Li, Lu & Huang 2020a). Immunological barriers preventing SARS-COV-2 infection and related damage include antiviral immune barriers such as antibody production by activated B cells (plasma cells), regulatory T cells, and the immunological effects conferred by IFN-α and IFN-β. In addition to the cell-mediated immunity conferred by NK cells and T cytotoxic cells, this response may eradicate SARS-CoV-2 virus infection (Bray, Sartain, Gollamudi & Rumbaut 2020).

Step 4. Cytokine storm-induced acute respiratory distress syndrome in COVID-19

Progression to acute respiratory distress syndrome then respiratory failure in COVID-19 patients may be due to massive host cytokine production (cytokines storm). This causes inflammation-induced tissue damage, increased capillary membrane permeability, pulmonary edema, and acute respiratory distress syndrome. Ultimately, the patients necessitate mechanical ventilation. Increased serum IL-6 (with an optimal predictive threshold at 80 pg/ml) is correlated with respiratory failure and the need for mechanical ventilation. Presence of associated comorbidities (diabetes mellitus, cancer, immunosuppressive therapy, and others), radiological findings, and rapid subsequent organ failure (Jiang, Yang, Sun, Chen, Ma, Yin, et al., 2018).

Step 5. Severe progression with shock

COVID-19 may present a variable clinical course. Respiratory impairment may be sudden due to overwhelming proinflammatory hypercytokinemia, multisystem tissue failure, respiratory failure (necessitating mechanical ventilation), and shock (Ragab, Salah Eldin, Taeimah, Khattab & Salem 2020).

Step 6. Septicemia and hypercoagulability

Severe cases of SARS-CoV-2 may involve hypercoagulable complications e.g. venous thromboembolism (e.g. cavernous sinus thrombosis) and pulmonary embolism. In addition, associated coagulation abnormalities may occur (Ragab et al., 2020). Thrombotic complications including increased D-dimer, manifest pulmonary embolism and venous thromboembolism may increase patient mortality in intensive care units (Middeldorp, Coppens, van Haaps, Foppen, Vlaar, Müller, et al., 2020). Hypercoagulability is a prothrombotic state exaggerated by tissue damage underlying vascular endothelial cells. The fibrin degradation product, D-dimer, correlates with SARS-CoV-2 severity. Serum D-dimer concentrations increased massively in patients with severe COVID-19 infection compared to those with mild or improved symptoms (Griffin, Jensen, Khan, Chin, Chin, Saad, et al., 2020). Macrophages produce the proinflammatory cytokine TNF-α during the inflammatory processes induced by SARS-CoV-2. This causes cell death through both necrotic and apoptotic pathways. TNF-α stimulates the activation of tissue factors and activation of the extrinsic pathway of coagulation, causing the production of cross-linked fibrin clots. This is followed by fibrinolysis mediated by tissue plasminogen activator. During acute inflammation caused by COVID-19, TNF-α increases while protein C level decreases, and this enhances the persistence of venous thromboembolism (Li, Zhao, Wei, Chen, Wang, Jia, et al., 2020b).

Step 7. COVID-19 mortality

Reported COVID-19 mortality rates are quite variable among countries and nations (ranging from 0.3 to 10%). The lowest rates of 2.5% and 4.0% in China and neighboring countries and increased to about 10% in Italy (which has the highest fatality rate) (Yuan, Li, Lv & Lu 2020), where the elderly (above 75 years) constituted a significant proportion of fatalities (about 85% of deaths due to the COVID-19 pandemic).

Gastrointestinal manifestations in the adult and pediatric population

Variable clinical presentations may be encountered in the course of SARS-CoV-2 infection. Gastrointestinal symptoms as nausea, abdominal pain, and diarrhea, are usually seen during COVID-19 pathogenesis and may contribute to

increased viral transmission (Galanopoulos, Gkeros, Doukatas, Karianakis, Pontas, Tsoukalas, et al., 2020).

Digestive symptoms e.g. diarrhea, are strongly related to a higher incidence of positive stool PCR swabs (about 48.1% of patients) for viral RNA. Affected patients may have a high viral load for SARS-CoV-2 RNA. The presence of viral RNA in stool was confirmed with a relatively long duration (33-47 days after the first onset of the disease). Unfortunately, stool samples remained positive even after viral clearance of nasal RT-PCR swabs (Galanopoulos et al. 2020; Cheung, Hung, Chan, Lung, Tso, Liu, et al., 2020).

Table 2. :Symptomatology of COVID-19

***Mild COVID-19 presentation**:

- Fever, cough, somnolence; drowsiness, diarrhea, nausea, vomiting, and abdominal pain.
- Anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, and headache.
- Upper respiratory symptoms (loss of taste, loss of smell, dry cough, nasal congestion and pharyngitis)

*** Moderate COVID-19 presentation:** high fever, lymphopenia, (leukopenia or leukocytosis), and high serum transaminases, **pneumonia, and bronchopneumonia (**requiring oxygen support).

***Severe COVID-19 presentation: Acute respiratory distress syndrome (ARDS):**

Bilateral lung opacities, lobar congestion, consolidation, collapse with massive lung collapse, or nodular lesions in chest radiographs or CT scans.

*** Gastrointestinal symptoms (17.6%):** usually deteriorate upon COVID-19 progression, indicating disease severity.

- Anorexia
- Diarrhea
- Liver impairment causing acute hepatitis or mild to moderate elevation of serum transaminases (ALT and AST).
- Nausea
- Abdominal pain

Pathophysiology of gastrointestinal and hepatic COVID-19

The mucus membranes and adjacent tissues in the esophagus, stomach, duodenum, and rectum exhibit edema with patchy infiltrations. Such infiltrations may be plasmacytic and lymphocytic. SARS-CoV-2-induced gastrointestinal symptoms may take place via direct virus invasion of digestive cells, immunological-mediated tissue damage, or end-organ tissue injury (Tian, Rong, Nian & He 2020). Attachment of SARS-CoV-2 to ACE2 receptors takes place using the viral spike proteins (Luan, Lu, Jin & Zhang 2020). This occurs 10-20-fold more than with the virus SARS-CoV-1. Such high infectivity may denote massive human-to-human transmission of SARS-CoV-2 (Gordon, Jang, Bouhaddou, Xu, Obernier, White, et al., 2020). The viral spike protein mediates SARS-CoV-2 attachment to the ACE2 receptor with secondary entry into the target digestive and hepatic cells. Such entry is facilitated by the patient's transmembrane serine protease 2. Serine protease 2 causes the viral spike protein to divide into two functional monomers: S1 and S2. The S1 monomer attaches the virus to the ACE2 receptor, while the S2 monomer mediates viral fusion with the target cell membrane with subsequent viral entry into the target cells (Hoffmann et al. 2020). This may support the use of protease inhibitors for future COVID-19 treatment.

ACE2 receptors are also present in gall bladder cells (cholangiocytes). This may lead to hepatobiliary infection and damage that may occur in an opposite direction to bile flow upon viral entry into the biliary tree (Zhang, Shi &Wang 2020). SARS-CoV-2 is still present in the stools of infected patients, implicating the possibility of

fecal-oral transmission. More attention should be given to monitoring liver function tests during COVID-19, particularly in patients with more disease severity (Gu et al. 2020, Lee, Huo and Huang 2020). Liver biopsies confirm the presence of RNA of SARS-COV-2 in hepatic cells. In addition, evidence of liver damage may take place e.g. apoptosis, lobular inflammation, acidophilic bodies, and cellular ballooning (Gu et al. 2020). Unfortunately, liver injury may be due to drugs given to COVID-19 patients such as NSAIDs, antibiotics, and antiretroviral medications. Moreover, the cytokine storm aggravates the production of pro-inflammatory cytokines, causing extensive cardio-pulmonary tissue damage, hypoxemia, hypoxia, and vascular thrombosis. All these complications may aggravate any underlying liver injury (Zhang et al. 2020).

ACE2 has a renin-angiotensin system-independent function that regulates intestinal neutral amino acid transporters facilitating decreased expression of antimicrobial peptides and gut microbiota. That facilitates intestinal inflammation and diarrhea (Syed, Khan, Gosai, Asif & Dhillon (2020).

COVID-19 and its impact on chronic liver diseases

Hepatitis B infection aggravates clinical outcomes in SARS-CoV-2 patients, causing extensive hepatic damage. Likewise, immunosuppressive medications given to cancer patients and people with autoimmune conditions may enhance COVID-19 infection, related tissue damage, and mortality. In the same context, it is quite advisable to screen liver donors and recipients for SARS-CoV-2 before a liver transplant to avoid transmitting the virus in the graft. Cancer patients and those with liver cirrhosis are more vulnerable to SARS-CoV-2 infection owing to their suppressed immunity (Zhang et al. 2020; Mao, Liang, Shen, Ghosh, Zhu, Yang, et al., 2020).

Pancreatic injury in COVID-19 infection

ACE2 receptors are highly expressed in pancreatic islet cells. SARS-CoV-2 may cause direct cytopathic effects, indirect systemic inflammation, or immune-mediated cellular effects. These collectively cause pancreatic damage and related enzyme abnormalities. NSAIDs and antipyretics may aggravate such tissue damage. 17% of COVID-19 patients got pancreatic injury (evidenced by increased serum amylase or lipase) that might result in the occurrence of acute diabetes (or abnormal blood glucose levels), but not reaching severe pancreatitis (Patel et al. 2020).

Antioxidant (e.g. glutathione) deficiency exaggerates SARS-CoV-2 infection (Figure 2)

The pathogenesis of COVID-19 and previous coronavirus infections (SARS-CoV-1 and MERS-CoV) involves the production of many proinflammatory cytokines, e.g. TNF-α, IL-8, IL-6, IL-7, IL-10, and others (Goyal, Choi, Pinheiro, Schenck, Chen, Jabri, et al., 2020). Angiotensin II is a potent activator of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and hence an inducer of reactive oxygen species (ROS) production. ACE2 receptors are common receptors for NADPH oxidase-4 (causing the generation of reactive oxygen species) (Samavati and Uhal 2020) and both SARS-CoV-1 and the novel SARS-CoV-2. Glycosylation of serum and tissue proteins occurs via a non-enzymatic reaction that commonly happens in diabetic subjects. ACE2 glycosylation is accelerated under hyperglycemic conditions and facilitates the attachment of the SARS-CoV-2 virus to target cells (Ceriello 2020). The cytokine storm during SARS-CoV-2 infection includes increased formation of proinflammatory cytokines such as IL-6, IL-2, IL-7, IL-10, and TNF-α levels, which are all associated with severe respiratory failure. This picture carries significant similarity to SARS-CoV-1 and MERS-CoV (Goyal et al. 2020).

The clinical deterioration of COVID-19 to acute respiratory distress syndrome is a product of cytokine storm. This is closely associated with increased serum IL-6 levels, extensive inflammatory reaction (increased pro-inflammatory vs. decreased anti-inflammatory cytokines), prolonged admission to the intensive care unit, progression to acute respiratory distress, and subsequent mortality. Reduced glutathione deficiency caused increased ROS levels and aggravated the severity of the clinical

manifestation of the COVID-19 pandemic. Likewise, high serum reduced glutathione caused decreased ROS and a shorter course of COVID-19 infection (Polonikov 2020).

Moreover, SARS-CoV-2 significantly suppresses the content of intracellular reduced glutathione levels by decreasing the activity of intracellular erythroid 2-related factor that stimulates reduced glutathione production. Interestingly, exogenous supplementation of reduced glutathione enhances immunity against different bacterial and viral infections. Liposomes containing reduced glutathione caused an improvement in cytokine response of Th1 lymphocytes in patients having human immunodeficiency virus and *Mycobacterium tuberculosis* infections (Guloyan, Oganesian, Baghdasaryan, Yeh, Singh, Guilford, et al., 2020). Interestingly, the intracellular reduced glutathione concentration in erythrocytes is suppressed in type II diabetic patients (Lutchmansingh, Hsu, Bennett, Badaloo, McFarlane-Anderson, Gordon-Strachan, et al., 2018). Thus, these high-risk or immunocompromised populations may strongly benefit from receiving liposomal reduced glutathione supplementation.

In addition, common COVID-19 presentations such as pneumonia, dysgeusia, and hyposmia scored immediate improvements upon treatment with N-acetyl cysteine (a precursor of reduced glutathione), oral or intravenous reduced glutathione intake, and α-lipoic acid (Pan, Ye, Sun, Gui, Liang, Li, et al., 2020). Dyspnea in some COVID-19 patients improved one hour after intake of reduced glutathione and continued to improve with subsequent doses. Patients' sense of well-being and improvements started to increase rapidly (Horowitz, Freeman & Bruzzese 2020). Liposomal drug formulations improve the delivery of hydrophilic and lipophilic substances to prevent drug load degradation (in acidic environments such as gastric luminal pH), drug inactivation, and drug dilution in the circulation (Mehta, Kulkarni, Nikam, Padya, Pandey & Mutalik 2021). Interestingly, supplementation of oral liposomal reduced glutathione to healthy adults caused increased levels of reduced glutathione (by 100%) in peripheral blood mononuclear cells with a concomitant decrease in the biomarkers used to track oxidative stress, e.g. 8-isoprostane and the oxidized glutathione/reduced glutathione ratio. Likewise, liposomes containing reduced glutathione and given orally caused increased cytotoxicity in natural killer cells (by 400%) within a relatively short period (2 weeks). This confirms that increasing the antioxidant power conferred decreased oxidative stress and increased immunity (Sinha, Sinha, Calcagnotto, Trushin, Haley, Schell, et al., 2018). Liposomes containing reduced glutathione supplementation is a highly advisable supplement for treating COVID-19 patients.

In COVID-19 patients, oxidative stress increases in the presence of associated comorbidities such as diabetes mellitus and rheumatoid arthritis. Liposomal glutathione intake may be more beneficial than N-acetyl L-cysteine supplementation, as the enzymes essential for the synthesis of glutathione from L-cysteine may be deficient in such comorbidities.

TaibUVID nutritional supplements enhance antioxidants and combat COVID-19

Adjuvant nutritional treatment is a commonly missed health factor when treating fatal viral diseases such as COVID-19. We recently introduced TaibUVID nutritional supplements, composed of six medicinal plants and natural products. TaibUVID components include *Nigella sativa*, chamomile, and natural honey. Adding clove was optional (El Sayed, Almaramhy, Aljehani, Okashah, El-Anzi, AlHarbi, et al., 2020c; El Sayed, Bahashwan, Aboonq, Baghdadi, Elshazley, Okashah, et al., 2020d; El Sayed, Aboonq, El Rashedy, Aljehani, Abou El-Magd, Okashah, El-Anzi, Alharbi, El-Tahlawi & Nabo 2020b &El Sayed, Aboonq, Aljehani, Hassan, Abou El-Magd, Abdelrahman, et al., 2020a). This is suggested for both treatment and prophylaxis of COVID-19. TaibUVID Forte adds Costus, senna, and fennel to TaibUVID. Many meta-analyses and systematic reviews have confirmed the therapeutic benefits of TaibUVID components in the management of many co-morbidities and human diseases, e.g. diabetes mellitus and hypertension that are commonly encountered in COVID-19 patients. TaibUVID, TaibUVID Forte and

TaibUVID inhalation therapies were quite effective in the management of the COVID-19 pandemic in addition to minimizing the morbidity period without causing any side effects (El Sayed et al. 2020d, El Sayed et al. 2020c, El Sayed et al. 2020b, El Sayed et al. 2020a).

Interestingly, all components of TaibUVID nutritional supplements cause increased glutathione. *Nigella sativa* fixed seeds and essential oil increase levels of reduced glutathione and related antioxidant enzymes (Abd-Elkareem, El-Rahman, Mokhless, Khalil & Amer 2021). Natural honey also increases reduced glutathione, antioxidant power, anti-inflammatory effects, and antiulcer potential against gastric ulcers in rats (Almasaudi, El-Shitany, Abbas, Abdel-Dayem, Ali, Al Jaouni et al., 2016). Senna results in increased activity of the antioxidant defense systems, including reduced glutathione (Coelho, Barbosa, Mito, Mantovanelli, Oliveira & Ishii-Iwamoto 2017). Fennel also increases the antioxidant power, the whole content of reduced glutathione and anticarcinogenic effects (Wang, Wang, Pan, Huang, Ren, Xu, et al., 2020d). Likewise, clove also increases the antioxidant power and reduces glutathione (Shekhar, Yadav, Singh, Pradhan, Desai, Dey et al., 2018). Moreover, chamomile (*Anthemis hyaline*) oil moderately ameliorated glutathione depletion (via increasing the reduced glutathione content) and the decrease in superoxide dismutase activity in the liver of acetaminophen-administered rats (Ebada 2018). Current therapeutics for COVID-19 may carry a lot of side effects due to free radicals generation that may deteriorate patients' condition and hence the bad need for adjuvant antioxidant therapies. Unfortunately, corticosteroids given to COVID-19 patients are known to decrease lymphocyte count which may aggravate the health status of the patients. Fortunately, this can be corrected by giving nigella sativa and natural honey that is contained in TaibUVID nutritional supplements. Natural antioxidants such as nigella sativa, honey, senna, fennel, and costus are recommended prophetic medicine remedies. Prophetic medicine is the medical knowledge gained from the sayings, deeds, and teachings of Prophet Muhammad peace be upon him.

Conclusion

COVID-19 is a devastating pandemic. Oxidant/antioxidant status is impaired in COVID-19 patients prone to depleted total antioxidant capacity. Decreased serum antioxidants can be regarded as a predictive marker of COVID-19 severity. COVID-19 patients had elevated levels of oxidative stress and reduction of antioxidant indices that aggravated the severity of COVID-19 in hospitalized patients. Gastrointestinal symptoms usually worsen with disease progression and include anorexia, diarrhea, liver injury, nausea, and abdominal pain. Cytokine storm-induced acute respiratory distress syndrome occurs in severe COVID-19 cases due to overwhelming proinflammatory hypercytokinemia and multisystem tissue damage. Antioxidant (e.g. glutathione) deficiency exaggerates SARS-CoV-2 infection. High serum-reduced glutathione causes decreased ROS and a shorter course of illness. Antioxidants are strongly suggested as adjuvant therapeutics to combat the pandemic. COVID-19 patients presenting with pneumonia, dysgeusia, and hyposmia scored immediate improvements upon treatment with the reduced glutathione precursor N-acetyl cysteine. In previous publications, we introduced TaibUVID antioxidant nutritional supplements that were found to be effective in helping COVID-19 patients recover.

Conflict of interest

The author declares that there is no conflict of interest.

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