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Review Article

COVID-19 Drugs and Glucose-6-phosphate Dehydrogenase Deficiency: A Matter of Life Threatening And Public Health

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ABSTRACT

Background: The current COVID-19 pandemic has created significant health consequences for the world population. Therapies and drugs are being continuously developed in an effort to implement the most effective treatment. G6PD deficiency is the most prevalent human enzymatic defect, affecting more than 500 million people worldwide, but is infrequently taken into consideration in healthcare practice. **Purpose:** The aim of this review is collecting and assembling the most relevant information about safety of current drugs and nutraceuticals, proposed or already used for COVID-19 treatment, with regard to G6PD deficient people, in order to know possible drug-induced adverse effects. **Methods:** An extensive literature search was performed through scientific papers, unsafe drug lists, drug datasheets, drug databases, National Public Health institutional websites. **Results:** Methylene blue, ozone, chloroquine and hydroxychloroquine administration should be avoided in G6PD deficient patients. The other reviewed drugs should be administered at therapeutic doses under medical supervision. **Conclusion:** The list of drugs and nutraceuticals for use in COVID-19 here provided, usefully brought to Healthcare personnel's and patients' awareness before any drug administration, may allow you to avoid or at least manage any possible drug-associated symptoms - particularly hemolytic crisis, which is a potentially fatal risk for G6PD deficient patients.

KEY POINTS

- This review collects and assembles the most relevant information about safety of current drugs and nutraceuticals for COVID-19 treatment, with regard to people with G6PD deficiency, to avoid any possible drug-associated adverse reactions.
- Methylene blue, ozone, chloroquine and hydroxychloroquine administration should be avoided in G6PD deficient patients.
- The other reviewed drugs should be administered at therapeutic doses under medical supervision.

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is currently the cause of an increasing numbers of deaths, due to high infectivity and respiratory and renal failure risk [1].

Glucose-6-Phosphate-Dehydrogenase (G6PD) deficiency is a X-linked disorder affecting more than 500 million people worldwide. G6PD enzymatic variants have different levels of enzyme activity and subsequent different clinical manifestations: Class I (10-20% of normal activity, severe deficiency), resulting in chronic hemolytic anemia; Class II (<10% of normal activity, very severe deficiency), resulting in risk of acute hemolytic anemia episodes; Class III, such as the G6PD A- (10-60% of normal activity, severe-to-moderate deficiency), resulting in rare cases of acute hemolytic anemia [2].

The ubiquitous G6PD enzyme catalyzes the initial step in the pentose phosphate pathway, generating Nicotinamide adenine dinucleotide phosphate (NADPH), in turn converting oxidized glutathione (GSSG) into reduced glutathione (GSH) and providing a protective effect against oxidative stress resulting from an excessive generation of reactive oxygen

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species (ROS), which can damage biological molecules and structures. Erythrocytes are protected by generating GSH via this pathway only [3]. Erythrocyte hemolysis can be caused by oxidative stress triggered by certain food such as fava beans, oxidative drugs, infections and other causes of oxidative stress [4]. Therefore, acute hemoglobin decrease in a COVID-19 patient may be a signal of G6PD deficiency.

G6PD deficiency has been proposed as one of the factors predisposing to more severe COVID-19 disease [4], e.g., by increasing vulnerability to coronavirus infection, where *in vitro* studies observed that G6PD deficient fibroblasts and G6PD knockdown cells derived from lung epithelium, infected with human coronavirus 229E (HCoV229E), exhibited not only higher coronavirus viral gene expression and viral particle production but also higher susceptibility to HCoV229E mediated cell death [5].

In the current pandemic context, with an increasing number of cases worldwide and often overloaded health systems, it is urgent not only to find effective treatments, but also to consider co-morbidity-related risk factors and unsafe treatments. Despite its high prevalence, G6PD deficiency is infrequently taken into consideration in healthcare practice, often increasing drug-associated hemolysis risk, thereby complicating patient's clinical outcome and contributing to the hospital overload.

Scientific journals, National Health departments and organizations have published information on the relationships between COVID-19 and G6PD deficiency, case reports and unsafe drug lists, but it is often dispersed and not easy to find. On this basis, this paper collects and assembles this information, reviewing the potential risks for G6PD deficient people as found in the scientific literature, with regard to current drugs and nutraceuticals proposed or already used for COVID-19 treatment, with recommendations from unsafe drug lists [6,7], warnings regarding their safety for G6PD deficient patients, and adverse reactions. The general therapeutical dosage of the mentioned drug, retrieved from drug datasheets, is shown at the bottom of each paragraph. A G6PD deficiency-specific therapeutic window for each drug appears difficult to be established so far, because of genotypic and phenotypic variability of this condition that would deserve specific pharmacogenomic studies.

This paper is aimed at healthcare personnel and patients as an aid providing rapid consultation before any drug administration against COVID-19, in order to avoid or at least manage any potential drug-associated symptoms specific for G6PD deficient patients, as has already been observed with chloroquine and hydroxychloroquine [8], particularly the potentially fatal hemolytic crisis.

METHODS

From March 2020 to July 2021 an extensive literature search was performed on scientific online databases such as PubMed, National Drug Databases and Public Health institutional websites, official lists of drugs potentially unsafe for G6PD deficient people, in order to retrieve the most relevant citations related to their use in COVID-19 treatment, safety and effects on G6PD deficient population.

The first phase of search was performed by combination of the keywords "COVID-19", "Drug", "Nutraceutical", "G6PD", "Favism", "Oxidative stress" in order to retrieve the most mentioned COVID-19 treatments, both proposed and actually used, and possible interactions with G6PD deficiency. The search was then refined in the second phase including both *in vitro*, *in vivo* and clinical studies for the short-listed agents by combination of the keyword "G6PD" and each keyword of the following: "ACE-inhibitors", "Antibiotic", "Antiviral", "Corticosteroid", "Monoclonal Antibody", "Non-Steroidal", "Ozone", "Statins", or each name of the drugs mentioned in the Table 1. The Table 1 contains name, function, mechanism of action and warnings about safety of the reviewed drugs and nutraceuticals used in COVID-19 regarding G6PD deficiency, ready-to-use for healthcare personnel and patients; the Table 2 contains the correspondence between the frequency definitions and the ratios of drug adverse effects according to the Council for International Organizations of Medical Sciences (CIOMS) guidelines [9].

After searching "COVID-19" on Pubmed database and then filtering by clinical trials, 900 results were retrieved; on the contrary, the search of "COVID-19 and G6PD and trial" gave 11 results about COVID-19, among them 4 were included as they actually involved COVID-19 patients with G6PD deficiency [10, 11, 12] or analyzed pharmacogenomics and COVID-19 also referred to G6PD deficiency [13], while the other studies used G6PD deficiency as an exclusion criterion.

After retrieval and in-depth study of more than 300 documents, the selection was refined by choosing 73 relevant and comprehensive references (mostly in English, one in French and 3 in Italian): 3 institutional reports, 2 official lists of drugs unsafe for G6PD deficient population, 5 institutional drug databases and related package leaflets, 3 single drug package leaflets; the remaining references were original research or review papers.

DRUGS FOR USE IN COVID-19

Angiotensin-Converting Enzyme inhibitors/Angiotensin II Receptor Blockers

Enalapril provoked uncommon adverse reactions such as anemia (also hemolytic or aplastic) and rare hemoglobin decrease [14, 15, 16]; some hemolysis cases in G6PD deficient patients have been reported [14]. *Perindopril* caused very rare hemolytic anemia cases in G6PD deficient patients and very rare cases of hemoglobin and hematocrit reduction [14, 15]. Preclinical studies on *Candesartan* showed erythrocytes, hemoglobin, hematocrit reduction at high doses [14]. *Losartan* caused common cases of anemia in patients with chronic heart failure, and unknown frequency anemia in post-marketing phase; rare cases of hemolysis and rhabdomyolysis at unknown frequency have been reported [14, 15, 16]. *Telmisartan* caused uncommon anemia cases and rare cases of hemoglobin level reduction [14, 15, 16]. *Valsartan* caused hemoglobin and hematocrit level reduction [14, 16], very rare erythrocytes damage and erythrocytes decrease at unknown frequency [15, 16].

Table 1. COVID-19 drugs and nutraceuticals versus safety for G6PD deficiency

COVID-19 DRUGS AND NUTRACEUTICALS VERSUS SAFETY FOR G6PD DEFICIENCY			
Drug/ Nutraceutical	**Function**	**Mechanism of action**	**Safety for G6PD deficiency**
Methylene Blue	Reducing agent, broad-spectrum antimicrobial, photosensitizer	Reduction from $Fe^{3+}$to Fe^{2+}; change in intracellular pH and redox state [8]; viral nucleic acid damage by ROS generation [37]	NO, high risk ☹
Chloroquine[a] Hydroxychloroquine[a]	Immunomodulator, anti-inflammatory, broad spectrum antiviral, antiparasitic	Viral entry and endocytosis inhibition via endosomal acidification inhibition; interference with terminal glycosylation of ACE2 receptor [1]	NO, medium risk ☹
Ozone	Oxidant agent, cytoprotective, immunomodulator, anti-oxidizing, anti-inflammatory, anti-viral	Viral inactivation by direct (O_3) or indirect oxidation (reactive oxygen species ROS and lipid oxidation products LOP); cellular and humoral immune system stimulation; inflammation reduction; antioxidant system modulation [50]	NO, medium risk ☹
Enalapril Perindopril	Anti-hypertensive	Angiotensin-Converting-Enzyme (ACE) inhibitors; interference with bond between ACE2 receptor and viral S protein [5]	YES, low risk 😐
Candesartan Losartan Telmisartan Valsartan		Angiotensin II receptor blockers; interference with bond between ACE2 receptor and viral S protein [5]	
Azithromycin	Broad spectrum antibiotic (bacteriostatic), immunomodulator, anti-inflammatory, antiviral	Rapid viral clearance [10]	YES, low risk 😐
Ivermectin	Broad-spectrum antiparasitic, antiviral, immunomodulator	Viral replication reducing and nuclear import of viral proteins inhibition[17]	YES, low risk 😐
Rapamycin (Sirolimus)[b]	Immunosuppressor, antiviral	FRAP-Mammalian target of rapamycin (mTOR) kinase inhibition, involved in viral replication [18]	YES, low risk 😐
Lopinavir+Ritonavir	Antiviral	Viral 3-chymotrypsin-like protease inhibitors[5]	YES, low risk 😐
Nitazoxanide	Antiviral, anti-inflammatory	Blockade of viral proteins intracellular movement and maturation; enhancement of IFN-1 production by host cell fibroblasts that may potentiate antiviral activity [1]	YES, low risk 😐
Oseltamivir	Antiviral	Viral neuraminidase inhibitor [1]	YES, low risk 😐
Ribavirin	Antiviral	Viral RNA-dependent RNA polymerase inhibitor [1]	YES, low risk 😐
Dexamethasone Methylprednisolone	Anti-inflammatory, immunosuppressors, immunomodulators	Glucocorticoid receptor agonist; inhibition of pro-inflammatory prostaglandins and leukotrienes biosynthesis [28]	YES, low risk 😐
Deferoxamine	Iron chelator, antioxidant immunomodulator, antiviral	Viral replication inhibition, decrease of oxidative stress and promotion of viral mutations via iron chelation [5]	YES, low risk 😐
Famotidine	Anti-acid, antioxidant	Histamine-2 receptor antagonist; viral replication inhibition [28,33]	YES, low risk 😐
Interferons IFNα2b, IFNα1a, IFNα1b	Broad-spectrum antiviral agent and signaling protein	Antiviral immune response boost in the early phase of the disease [1]	YES, low risk 😐

(Contd...)

Table 1. *(Continued)*

COVID-19 DRUGS AND NUTRACEUTICALS VERSUS SAFETY FOR G6PD DEFICIENCY			
Drug/ Nutraceutical	**Function**	**Mechanism of action**	**Safety for G6PD deficiency**
Baricitinib	Anti-inflammatory, immune suppressor, endocytosis inhibitor	Janus Kinases 1 and 2 inhibitor; viral entry via clathrin-mediated endocytosis and intracellular viral particle assembly prevention; hyperinflammatory state reduction [1]	YES, low risk 😐
Ruxolitinib	Anti-inflammatory, immune suppressor	Janus Kinases 1 and 2 inhibitor; pro-inflam-matory cytokines secretion decrease [42]	YES, low risk 😐
Tocilizumab	Anti-inflammatory, immune suppressor	Interleukin-6 receptor antagonist following inflammatory factors and signaling cascade blockade [1]	YES, low risk 😐
Ibuprofen Acetaminophen[c] (Paracetamol) [b] Colchicine[c] Indomethacin	Inflammation inhibitor and immunosuppressor, analgesic, immunomodulator, antipyretic	Cyclooxygenase 1 and 2 inhibitors and subsequent prostaglandins synthesis inhibition [48] Inflammasome complex blockade [48] Viral RNA synthesis inhibition; viral entry and endocytosis inhibition	YES, low risk 😐
Zinc	Anti-oxidant, antibacterial, antifungal, antiviral, anti-inflammatory	RNA polymerase activity inhibition; chloroquine intracellular uptake enhancement [5][53]	YES, low risk 😐
Copper	Anti-inflammatory and immunomodulatory	Inflammation decrease [53][57]	YES, low risk 😐
Atorvastatin Pravastatin	Anti-dyslipidemia, anti-inflammatory, antithrombotic, immunomodulatory	HMG-CoA reductase inhibitors, reduced C-reactive protein, endothelial function improvement [51]	YES, low risk 😐
Vitamin B1 (Thiamine) [b]	Anti-oxidant, immune modulator, metabolic co-enzyme	Suppression of oxidative stress-induced NF-kB activation [28][5]	YES, low risk 😐
Vitamin C[c] (Ascorbic acid) [b]	Anti-oxidant, immune modulator	Cytokine storm downregulation; endothelium protection from oxidant injury and support to tissue repair [5, 28]	YES, low risk 😐
A-Lipoic Acid	Antibiotic (bacteriostatic), cellular coenzyme, antioxidant	Viral replication inhibition, ROS scavenging [5]	YES 🙂
Remdesivir	Antiviral	Viral RNA-dependent RNA polymerase inhibitor [1]	YES 🙂
Convalescent plasma or passive immunotherapy	Specific immune response, anticoagulant	Immune system restoration virus neutralization to suppress viremia [1]	YES 🙂
Heparin	Anticoagulant and anti-inflammatory	Thrombosis prophylaxis/treatment [5]	YES 🙂
Melatonin	Anti-inflammatory, anti-oxidant, circadian rhythm regulator	Immune cell phenotype regulation; ROS scavenging, anti-oxidative enzyme up-regulation, pro-oxidative enzymes down-regulation [36]	YES 🙂
Magnesium	Anti-oxidant, antibacterial, antifungal, antiviral, anti-inflammatory	Innate and adaptative immune system modulator, T-cell activation, inflammation response limitation; vasodilation and bronchodilation [61, 62]	YES 🙂
Anakinra Emapalumab	Anti-inflammatory, immune suppressors	IL-1 receptor antagonist [42] IFN-γ antagonist	YES 🙂

(Contd...)

Table 1. *(Continued)*

COVID-19 DRUGS AND NUTRACEUTICALS VERSUS SAFETY FOR G6PD DEFICIENCY			
Drug/ Nutraceutical	**Function**	**Mechanism of action**	**Safety for G6PD deficiency**
N-Acetylcysteine	Anti-oxidant, anti-inflammatory, mucolytic	ROS scavenger, oxidative stress decrease, inflammatory response modulation [57,12]	YES ☺
Vitamins A	Anti-oxidant, immune stimulator	Innate immune response up-regulation in uninfected bystander cells, making them refractory to productive viral infection; ROS scavenger, oxidative stress decrease [5]	YES ☺
Vitamin B12	Immunomodulator	Prevention of excessive immune reaction [61]	YES ☺
Vitamin D	Immune stimulator	Stimulation of immune cell maturation [5][53]	YES ☺
Vitamin E	Anti-oxidant	ROS scavenger, oxidative stress decrease [5][53]	YES ☺

[a] Not recommended, medium risk at therapeutic doses [6,7].
[b] Alternative name.
[c] Low risk at therapeutic doses [6,7].
Legend: Drugs and nutraceuticals proposed or already used for COVID-19 with a brief description of mechanism of action. On the right there are warnings about potential risks for G6PD deficient patients.
YES – happy face = no reported adverse reactions for G6PD deficient patients to date; drugs/nutraceuticals not mentioned in unsafe drug lists [6,7].
YES, low risk – serious face = several reports of clinical or preclinical adverse reactions or oxidant/hemolytic effects considered unsafe for G6PD deficient patients. However, in general these drugs/nutraceuticals can be used with vigilance at therapeutic doses; drugs/nutraceuticals not mentioned in unsafe drug lists [6,7] unless otherwise indicated.
NO, medium risk – sad face = strong oxidative potential, reports of several clinical or preclinical adverse reactions or oxidant/hemolytic effects considered dangerous for G6PD deficient patients; drugs/nutraceuticals not mentioned in unsafe drug lists [6,7] unless otherwise indicated.
NO, high risk – sad face = several reports of clinical or preclinical adverse reactions or oxidant/hemolytic effects, unsafe for G6PD deficient patients, thereby these drugs/nutraceuticals are contra-indicated in unsafe drug lists [6,7].
Please note that YES and happy face do not mean necessary that the drug is completely safe but only that no adverse reactions have been reported to date. It is hence necessary to use them with vigilance and caution in all cases.

Table 2. Frequency of adverse drug reactions

Frequency of adverse drug reactions	Cases/Exposed Ratio
Very common	≥1/10
Common	<1/10, ≥1/100
Uncommon	<1/100, ≥1/1000
Rare	<1/1000, ≥1/10000
Very rare	<1/10000

Legend: Frequency of adverse drug reactions (CIOMS, Council of International Organizations of Medical Sciences) [9].

Therapeutical dosage *per os* (PO): candesartan 4-8 mg/day; enalapril 2.5-5 mg/day, max 40 mg/day; perindopril 4-8 mg/day; losartan 50-100 mg/day; telmisartan 20-80 mg/day; valsartan 80-320 mg/day [14].

Antibiotics (macrolides)

Azithromycin triggers uncommon cases of hemolytic anemia [14]. *Ivermectin* seems to dysregulate genes connected with increased ROS production *in vitro*, such as Signal transducer and activator of transcription 1 (STAT1) and its downstream targets Interferon induced protein with tetratricopeptide repeats 3 (IFIT3), 2'-5'-Oligoadenylate Synthetase 1 (OAS1) and Tripartite Motif Containing 22 (TRIM22), with a negative effect on mitochondrial function [17]. *Rapamycin* caused very common cases of anemia and common cases of uremic-hemolytic syndrome [14, 16] and blocks insulin-driven G6PD enzyme induction via Phosphoinositide 3-kinase (PI-3K) and Mammalian target of rapamycin (MTOR) metabolic pathways *in vitro* [18]. *Spiramycin* is not-recommended for G6PD deficient patients [6,7].

Therapeutical dosage (PO): rapamycin 6 mg/day; azithromycin 500 mg/day [14]. Ivermectin administered even up to 120 mg (~2 m/kg) has provoked no severe adverse reactions in 68 healthy volunteers of a double-blind placebo-controlled study [17].

Antivirals

Lopinavir/Ritonavir (LTV/RTV), HIV protease inhibitors, may be contra-indicated in G6PD deficient patients because of common adverse reactions such as anemia. Other protein inhibitors such as Darunavir also contain potentially hemolytic sulfonamide. However, a retrospective study on 137 patients (11 with G6PD deficiency) treated with protease inhibitors found no hemolytic anemia cases [19]. LTV/RTV stimulated a significant ROS production increase, caused

mitochondrial network damage and induced caspase-independent cell apoptosis *in vitro* [20]. *In vitro* LTV treatment of erythrocytes from healthy volunteers induced eryptosis, partly caused by stimulation of ROS formation and Ca^{2+} entry [21]. Common cases of erythrocyte decrease have been reported [16].

Nitazoxanide can stimulate eryptosis *in vitro*, with cell membrane scrambling and cell shrinkage that may cause anemia; on the contrary, *in vitro* and *in vivo* studies suggested that erythrocyte clearance by eryptosis, with subsequent removal of eryptotic cells via phagocytosis, may prevent defective erythrocyte lysis before cell membrane rupture and protect against hemolysis, which leads erythrocytes to release their intracellular content into the blood [22]. *Oseltamivir* treatment reduced superoxide dismutase and catalase hepatic activities, and caused oxidative stress and hepatic acute toxicity *in vivo* [23]. *Ribavirin* has been associated with hemolysis (in 76%) and hemoglobin level decrease (in 49%) in a retrospective case series involving 126 adult patients treated with ribavirin during SARS epidemic in 2003 [5]. When used for SARS, clinical studies and meta-analyses showed that the most common adverse effect was hemolytic anemia (61% out of 110 patients treated with ribavirin), occurred after 3-5 days of therapy with doses above 1–2 g [1]. No significant hemolytic anemia worsening was detected in a prospective study involving 26 G6PD deficient patients treated for Hepatitis C Virus with orally administration 800-1200 mg/day [24]. Ribavirin is contra-indicated for patients with blood diseases because it triggers hemolytic anemia with very common case frequency; in combination with IFNa it may cause aplastic anemia and pure erythrocyte aplasia [14, 16]. *Remdesivir* has not been reported to cause any statistically significant clinical side effects specific for G6PD deficient patients so far [25].

Therapeutical dosage (PO): ribavirin 800 mg/day; LPV/RTV 200-800 mg/day; oseltamivir: 75-150 mg/day [14].

Chloroquine and Hydroxychloroquine

Some reports described hemolysis in G6PD-deficient patients caused by antimalarial drugs such as *chloroquine* (CQ). Its molecular variant *hydroxychloroquine* (HCQ) is better tolerated; nevertheless, an acute hemolytic episode was reported in a hospitalized COVID-19 patient, 72-year-old Caucasian man carrying G6PD deficiency (probably Mediterranean variant or Class II), after treatment with HCQ and lopinavir [4, 26]. Typically, CQ in itself does not cause hemolytic crisis but can trigger oxidative hemolytic crisis in association with infectious processes and feverish states on exposure to high doses, especially in G6PD deficient patients, as described in a case report of a 68-year-old Congolese man with comorbidities, hospitalized for COVID-19 infection, to whom a 600 mg single dose HCQ was given on day 6, triggering the hemolytic crisis and leading to the diagnosis of previously unknown G6PD deficiency (probably African variant or Class III) [8]; these evidences lead to hypothesize similar mechanisms in this patients' subset if affected by COVID-19 [4]. However, little data demonstrate this risk to date [1]. In a case report, a hospitalized COVID-19-positive Cameroonian 65-year-old man with comorbidities was observed to undergo a drug-induced acute hemolysis after administration of HCQ (400 mg BID, i.e., twice/day, day 1 and 200 mg BID day 2–5) in combination with azithromycin (500 mg day 1 and 250 mg day 2–5), stopped after 5 days; the patient was then diagnosed for G6PD deficiency (probably African variant or Class III) [10]. CQ has caused rare adverse reactions such as pancytopenia [14] and bone marrow depression, including anemia, aplastic anemia and hemolytic anemia in G6PD deficient patients [16]. HCQ has caused rare severe reduction in blood counts such as bone marrow depression, aplastic anemia and hemolytic anemia in G6PD deficient patients [14].

Although few studies performed about CQ and HQ effects on G6PD deficient people demonstrate their unsafety, these drugs should be avoided or at least used with caution, waiting for more statistically significant data.

Therapeutical dosage (PO): CQ 310 mg (single dose)/week (maximum 50 g); HCQ 400-600 mg/day [14].

Convalescent Plasma or Passive Immunotherapy

Whole blood, plasma reduced erythrocytes or plasma are routinely transfused to G6PD deficient patients for acute hemolysis crisis treatment, avoiding use of G6PD deficient donor blood; exchange transfusion is indicated for kernicterus, neonatal hemolysis, G6PD deficiency [27]. Convalescent plasma has not been reported to cause any side effects specific for G6PD deficient patients so far.

Corticosteroids

According to observational studies (83 and 101 hospitalized patients), *in silico* and *in vitro* studies, one of the few drugs to have proven benefit in severe COVID-19 are glucocorticoids, especially to limit cytokine storm, when used in the pulmonary phase but not in the viral replicative phase; the RECOVERY randomized trial, involving 2104 patients with administration of dexamethasone (6 mg daily for up to 10 days), showed that the patients receiving mechanical ventilation underwent a more marked mortality reduction when received dexamethasone, while the patients without respiratory failure underwent a worse outcome [28]. A protocol implementing this treatment is the MATH+ protocol [28], examined with regard to G6PD deficiency in the Table 3, that contains names, administration and warnings about safety of drugs and nutraceuticals used in the protocol, which has had notable success in treating COVID-19 and recommends use of glucocorticoids only for patients with respiratory failure.

In vitro and *in vivo* studies suggest that *dexamethasone* inhibits G6PD enzyme activity and can lead to oxidative stress by modifying the activity of antioxidant enzymatic systems [29]. On the contrary, glucocorticoid steroid *methylprednisolone* was found to have significant antioxidant activities and improve spinal cord injury patients' recovery in the multicenter NASCIS II and III randomized clinical trials, involving 162 and 499 patients respectively, [30], therefore

Table 3. MATH+protocol and G6PD deficiency

MATH+PROTOCOL AND G6PD DEFICIENCY		
Drug/Nutraceutical	**Administration**	**Safety for G6PD deficiency**
1) **M**ethylprednisolone	80 mg loading dose, followed by 40 mg q 12 hourly for at least 7 days	YES, low risk 😐
2) **A**scorbic acid[a] (Vitamin C) [b]	3 g IV q 6 hourly for at least 7 days (general population) or up to 6 g/day in divided doses (G6PD deficient patients)	YES, low risk 😐
3) **T**hiamine (Vitamin B1) [b]	200 mg IV q 12 hourly for at least 7 days	YES, low risk 😐
4) **H**eparin	Enoxaparin, i.e. 1 mg kg s/c q 12 hourly (dose adjust with CrCl<30 ml/min) Unfractionated heparin is suggested with CrCl<15 ml/min	YES 🙂
+ Melatonin	6–12 mg at night	YES 🙂
+ Famotidine	40 mg/day	YES, low risk 😐
+ Vitamin D	2000–4000 u/day PO	YES 🙂
+ Zinc	50–75 mg/day	YES, low risk 😐
+ Magnesium	2g IV for ICU patients only	YES 🙂
+ Atorvastatin	80 mg/day	YES, low risk 😐

[a] Low risk at therapeutic doses [6,7].
[b] Alternative name.
Legend: MATH+ protocol: Methylprednisolone, Ascorbic Acid, Thiamine, Heparin and supplements. This protocol has been proposed and implemented to treat COVID-19. For specific indications, check the original protocol [28].
On the right there are warnings about potential risks for G6PD deficient patients.
YES – happy face = no adverse reactions indicating lack of safety for G6PD deficient patients to date. These drugs/nutraceuticals are not mentioned in unsafe drug lists [6,7].
YES, low risk – serious face = several reported clinical or preclinical adverse reactions or oxidant/hemolytic effects, and hence considered unsafe for G6PD deficient patients. However, these drugs/nutraceuticals may possibly be administered at therapeutic doses. These drugs/nutraceuticals are not mentioned in unsafe drug lists [6,7], unless otherwise indicated.
Please note that YES and happy face do not necessarily mean that the drug is completely safe, only that no adverse reactions have been reported to date. It is necessary to use them with vigilance and caution in all cases.

it may be suggested as a possible alternative therapy for G6PD deficient patients.

Therapeutical dosage intramuscular or intravenous (IM or IV): dexamethasone 1 mg - 80 mg/day; methylprednisolone 10 mg - 1 g/day [14].

Deferoxamine

A significant decrease of H_2O_2-induced oxidative hemolysis was observed in erythrocytes cells with *deferoxamine* administration *in vitro*, as iron enhances ROS generation [31]. Deferoxamine treatment reduced blood transfusion necessity and shortened the clinical course of acute hemolytic crisis in all the G6PD deficient patients (80 out of 167 children) that received a single dose of deferoxamine (30–40 mg/kg IV) [32]. Deferoxamine is associated with very rare adverse reactions, such as low blood cell counts, and rare blood abnormalities [14].

Therapeutical dosage (IM) 2g, (IV) 15 mg/kg per day (maximum 80 mg/kg per day) [14].

Famotidine

Famotidine in combination with gallic acid had a synergistic antioxidant activity against oxidative stress related peptic ulcers *in vivo*, increasing antioxidant enzymes (superoxide dismutase, catalase, glutathione reductase, G6PD) while decreasing lipid peroxidation and myeloperoxidase [33]. Famotidine, although ineffective against superoxide anion and hydrogen peroxide, could scavenge hydroxyl radicals *in vivo*, such as hypochlorous acid and monochloramine, cytotoxic oxidants arising from inflammatory cells. On this basis, famotidine was suggested for use for peptic ulcer and other diseases characterized by free radical-mediated oxidative stress [34]; nevertheless, it also reported hematologic adverse reactions, such as very rare cases of pancytopenia [14].

Therapeutical dosage (PO): 40-80 mg/day [14].

Heparin

Heparin has been reported to have no contraindications for G6PD deficient patients so far.

Therapeutical dosage (IV): 1000 UI/day [14].

Interferons

Interferons reported adverse reactions such as myelosuppression, with temporary reduction in the blood cell production, causing hemoglobin decrease and subsequent anemia, typically stable and limited [1]. Peginterferon *IFNa2b* showed very common (specifically >25%) reported cases of anemia, common cases of hemolytic anemia, rare cases of rhabdomyolysis, very rare cases of aplastic anemia; mild-to-moderate reversible anemia occurred when peginterferon IFNa2b was used in combination with ribavirin, of greater severity than that produced by each active substance alone [14, 35]. *IFNb1a* may decrease erythrocytes, leukocytes or platelets levels individually (very common), or all together (rare) [14]; *IFNb1b* may decrease erythrocytes levels (anemia, common) [14, 16].

Therapeutical dosage subcutaneous (SC): IFNa 3 million UI 3 times per week, IFNa2b 1.5 mg/kg per week, IFNb1a 22-44 mg 3 times per week, IFNb1b 250 mg every 2 days [14].

Melatonin

Melatonin has indirect antiviral actions since exerts an antioxidant function, directly interacting with free radicals as a scavenger, upregulating activity of superoxide dismutase and other antioxidative enzymes (such as G6PD and glutathione reductase), down-regulating nitric oxide synthase and other pro-oxidative enzymes, as described in many *in vitro* and *in vivo* studies; all the 70 HSV-1 infected patients, treated with melatonin plus an extract of Aspergillus sp. with anti-herpetic properties, showed a higher percent of a complete regression of symptoms in a single blind randomized study, compared with the treatment with acyclovir alone [36].

On this basis, melatonin is suggested to have pharmacological utility in G6PD deficient patients at risk of hemolytic anemia, especially in the presence of infectious diseases.

Therapeutical dosage (PO): 2 mg/day [14].

Methylene Blue

Visible light excites *methylene blue*, enabling it to react with atmospheric oxygen (dioxygen, $3O_2$), leading to ROS (e.g., singlet oxygen $1O_2$ and hydrogen peroxide), biomolecule oxidation and consequent cell and tissue damage, as described in *in vitro* and *in vivo* studies [37].

As a case report showed, a 54-year-old COVID-19 patient with methemoglobinemia and a history of uncomplicated diabetes mellitus received azithromycin on hospital day 1, HCQ on hospital day 2 and, after a worsening respiratory failure on hospital day 4, 1.8 mg/kg of methylene blue, in order to contain his Met-Hb levels; nevertheless, hemolysis worsened, Met-Hb increased further to 18.8% and the patient passed away shortly [38]. The patient had showed hemolysis even before administration of methylene blue; therefore, this fatal outcome may have been related to the oxidizing effect of HCQ (since azithromycin is not known to be an oxidizing agent) or to COVID-19 infection; before his decease, the patient had been finally diagnosed with G6PD deficiency [38]. Methemoglobinemia consists in the presence of oxidized iron (from the ferrous Fe^{2+} to the ferric Fe^{3+} form) in the porphyrin group of heme irreversibly bound to the oxygen, and can be acquired mostly following administration of oxidizing medications (e.g., antimalarial drugs such as CQ) [38].

Methylene blue administration at a lower dose, with continuous monitoring, may be used in cases of mild-to-moderate G6PD deficiency without detectable hemolysis in order to treat methemoglobinemia, as described in *in vitro* studies, but it has been also known to be ineffective (since it requires NADPH, produced by G6PD that is low or absent in people with deficiency) and to increase oxidative stress and subsequent hemolysis severity, as described in observational studies on infants [39]. Nevertheless, methylene blue increases risk of hemolytic anemia and methemoglobinemia (with doses ≥7 mg/kg) and has been considered contraindicated for G6PD deficient patients [14].

On this basis, methylene blue administration should be avoided in G6PD deficient patients, especially in case of viral infections and other conditions that provoke further oxidative stress.

Therapeutical dosage (IV): 1-2 mg/kg (maximum 7 mg/kg) [14].

Monoclonal Antibodies

Anakinra and *emapalumab* has not been correlated to any side effects specific for G6PD deficient patients so far. Before *baricitinib* administration it is recommended to confirm absence of anemia in order to avoid drug-induced adverse reactions [14, 16]. Clinical baricitinib treatment caused dose-related changes in multiple laboratory measurements, many of which reported with other Janus Kinase (JAK)-inhibitors, including decreases in hemoglobin. Many clinical trials and observations suggested that Baricitinib administration should not be started and therapy should be interrupted with hemoglobin < 8 g/dL [40, 41]. Anemia and decrease of hemoglobin levels up to 8 g/dL were reported in clinical trials. Baricitinib exposure may be increased with co-administration of probenecid (contraindicated for G6PD deficient patients) [14], thereby these two drugs taken together could cause hemolysis in G6PD deficient patients. Baricitinib is a structural analog of *ruxolitinib*, which has been reported to cause common hematological adverse effects such as anemia, bleeding, thrombocytopenia and neutropenia at a dose of 20 mg/day in clinical studies [14, 42, 43], common cases of pancytopenia [16] and trigger of anemia via eryptosis *in vitro* (with typical events such as erythrocyte cell shrinkage and membrane phospholipid scrambling) [44]. *Tocilizumab* exerts an antioxidant role in rheumatoid arthritis treatment of patients [45] but showed hematologic adverse reactions: very rare cases of erythrocytes, leukocytes and platelets levels reduction have been reported [14, 16].

Therapeutical dosage: Anakinra 20-100 mg/day (SC); Baricitinib 2-4 mg/day (PO); ruxolitinib 10-50 mg/day (PO); tocilizumab 4-8 mg/kg (IV) [14]; Emapalumab 1 mg/kg every 3-4 days (IV) [46].

Non-steroidal Anti-inflammatory Drugs

After *colchicine* administration, rare adverse reactions have been reported, such as epistaxis and hemolytic or aplastic anemia [14] and rhabdomyolysis at unknown frequency [16]. *In vitro* studies on G6PD deficient erythrocytes showed that *ibuprofen* did not produce either statistically significant G6PD level decrease or hemolysis; furthermore, it seems to be well tolerated by G6PD patients, as showed in a clinical study involving 19 young females (aged 4 months-13 years and carrying intermediate erythrocyte G6PD deficiency), 14 males (aged 6 months-16 years, hemizygote), and one dizygotic and completely deficient female [19]. However, hematologic adverse reactions have been reported following ibuprofen administration, such as aplastic and hemolytic anemia, also reported following *indomethacin* administration [14].

Before *acetaminophen (paracetamol)* intake it is recommended to seek a medical evaluation because of reported cases of hemolytic anemia [14]. *In vitro* study and some case reports demonstrated acetaminophen hemolyzing effect, e. g. in a 16-year-old-male with G6PD deficiency that ingested an unknown amount of acetaminophen [19]. Another *in vitro* study reported acetaminophen-induced hemolysis on 10% of treated G6PD deficient erythrocytes only at high doses, 3000 mg daily for 14 days. Therefore, several authors consider acetaminophen harmless when given to G6PD deficient patients at therapeutic doses [47]. Short-term administration of acetaminophen and ibuprofen at therapeutic dosages did not increase hemolysis risk in 10 G6PD deficient male infants (mean age, 4.3 ± 1.3 years) in a prospective study [48].

Although G6PD deficient people are at increased risk of developing hemolytic anemia when exposed to oxidizing stresses, the use of non-steroidal anti-inflammatory drugs (NSAIDs) does not appear to increase this risk significantly. All these reports suggest to use NSAIDs with caution in G6PD deficient patients, ceasing administration in case of hemolytic crisis.

Therapeutical dosage (PO): colchicine 1-3 mg/day, ibuprofen 400-1800 mg/day, indomethacin 100-200 mg/day, acetaminophen 500-3000 mg/day [14].

Ozone

Ozone is an oxidizing molecule capable of decreasing organ damage caused by inflammation and oxidative stress by reacting with blood components to generate chemical messengers responsible for activating immune response, oxygen delivery, antioxidant enzymes induction and other biological functions. Although in the past G6PD deficient people were identified as a potential high-risk population with regard to elevated ambient ozone exposure, *in vitro* studies on human G6PD deficient (A- variant) erythrocytes and animal models demonstrated no risk of adverse G6PD deficiency-specific hematologic effects caused by either direct exposure or inhalation of oxidant gases (ozone and nitrogen dioxide) at ambient levels [49]; more studies should be also performed on more severe G6PD variants.

In vitro, *in vivo* studies and case reports showed that ozone improves oxygen metabolism, circulation and perfusion in hypoxic organs; in ozonized erythrocytes, glycolysis improves, Adenosine triphosphate (ATP) and 2,3- diphosphoglycerate levels increase, leading to HbO_2 dissociation curve shift to the right, arterial partial oxygen pressure (PO_2) increase, and venous PO_2 decrease, oxygen supply increase to ischemic tissues. Chronic exposure to ozone stimulates the bone marrow to generate new "gifted erythrocytes" better able to stretch and bend into the blood capillaries and to deliver oxygen. 2,3- diphosphoglycerate and G6PD levels increase, with subsequent tissues recovery to a normoxic state. Ozone protects against oxidative damage in the heart, liver, lung, and kidney tissues [50].

Despite its strong oxidative potential, ozone exposure has not been proved to be dangerous for G6PD deficient people so far; nevertheless, since little studies have been performed about ozone effects on G6PD deficient people, it should be avoided or at least used with caution.

Therapeutic window is 10-80 mg/ml (inhaled), but ozone generators release concentrations from 1 to 70–100 mg/ml; administrable by systemic or non-systemic techniques [50].

Statins

Chronic treatment with *pravastatin* induces liver mitochondrial redox imbalance, a potential cause of hepatic adverse reactions, as observed in animal models of human familial hypercholesterolemia: in particular, increased G6PD activity (44%) in the livers of treated mice, higher H_2O_2 production rate (40%), lower activity of aconitase (a superoxide-sensitive Krebs cycle enzyme) (28%). Reduced glutathione content and reduced-to-oxidized glutathione ratio were increased in livers of pravastatin treated mice (1.5- and 2-fold, respectively). Noteworthy, diet supplementation with the antioxidants Coenzyme Q10 (CoQ10) or creatine fully reversed all pravastatin effects *in vivo* [50]. Statin-induced oxidative stress may act via several Cytochrome P450 (CYP450) enzymes, involved in statin metabolism, in *in vitro* and *in vivo* experimental models [52].

The excessive or long-term use of statins was found to provoke cytotoxicity *in vitro*, hepatic and kidney damage, myopathy *in vivo* (also in humans) and oxidative stress, muscle toxicities such as rhabdomyolysis [52] observed with *atorvastatin* alone (rare) or in combination with fusidic acid, pravastatin alone (very rare), with statins in general in combination with azithromycin (uncommon) [14]. Certain predisposing factors, such as G6PD deficiency, may increase risk of rhabdomyolysis and impair patient's clinical outcome, as showed in a case report involving a 2-year-old African-American male patient with sickle cell trait, with a diagnosis of previously unknown G6PD deficiency [3], even more so if there is a concurrent condition with COVID-19 or if rhabdomyolysis represents an initial presentation of COVID-19.

Therapeutical dosage (PO): atorvastatin 10-80 mg/day, pravastatin 10-40 mg/day [14].

NUTRACEUTICALS FOR USE IN COVID-19

Several dietary supplements have been proposed in addition to pharmacological therapy in order to enhance drug effects and immune response, and to limit oxidative damage which occurs in COVID-19 patients [53].

Alpha-Lipoic Acid

Alpha-Lipoic Acid (ALA) regenerates other antioxidants (e.g., vitamins E and C) and plays a critical role in scavenging free radicals, enhancing intracellular glutathione (GSH) levels, as showed in *in vitro* and *in vivo* studies [5], preventing oxidative damage in several diseases and modulating the blood redox status, with benefit for G6PD deficient patients [54]. ALA supplementation (600 mg/day) was evaluated in a placebo-controlled randomized clinical trial (NCT02937363), involving 8 G6PD deficient male adults without any adverse events, and was found to enhance antioxidant status in G6PD deficient people without affecting redox responses to acute exercise, restoring blood antioxidant enzyme levels and managing G6PD deficient people's susceptibility to oxidative damage [54]. G6PD deficient cells are more susceptible to human coronavirus 229E *in vitro* but ALA supplementation has been shown to attenuate increased susceptibility in G6PD-knockdown cells [5].

Therapeutical dosage (PO): 200-1800 mg/day [55].

Minerals

Trace elements can play an active role on normal hematopoiesis and in G6PD deficiency-induced acute hemolytic anemia, as suggested by a clinical study involving 69 G6PD deficient and 61 age- matched G6PD normal adults: the G6PD deficient female adults had significantly lower serum magnesium levels and the G6PD deficient male adults had significantly higher levels of serum copper and magnesium than those of the respective control group [56].

Alteration in immune responses and decrease in infection frequency have been correlated with *copper* deficiency, observed in *in vivo* studies, following chronic TNF-induced lung inflammation, potentially limited by copper supplementation [53], which may exert an anti-inflammatory role in human viral infections such as COVID-19 [56]. In a clinical study on 9 men, a copper dose of 7.8 mg/day reduced oxidative stress and altered immune function [58]. Orally ingested copper Cu (II) (0.25 to 1.0 mg) is usually safe also at high concentrations, but several patient subsets such as patients with Wilson's disease or with G6PD deficiency may suffer the risk of hemolytic anemia. *In vitro* studies demonstrated that G6PD deficient erythrocytes, exposed to copper, increased methemoglobin and decreased GSH in comparison with normal erythrocytes. Ingestion of both copper and chlorite combined may represent an increased risk for G6PD deficient individuals [59]. Cu exposure decreases lipid contents in liver and adipose tissues via reducing lipogenic enzymes (such as G6PD) activities and mRNA expression in an animal model in a tissue-specific and dose-dependent manner [60].

Magnesium (Mg^{2+}) has antihypertensive, antithrombotic, and bronchodilator properties. In a cohort observational study on 43 patients, 150 mg/d oral magnesium, 1000 IU/d oral vitamin D3, and 500 mcg/d oral vitamin B12 given to 17 COVID-19 patients ≥50 y of age significantly reduced proportion of patients with COVID-19 progression to severe disease [61].

According to *in vitro* studies, magnesium deficiency promotes oxidative stress in endothelial cells, leading to increased cytotoxicity and ROS production, whereas high intracellular Mg^{2+} increases endothelial nitric oxide synthase (NOS) activity and suppresses the synthesis of vasoconstrictor endothelin-1. When low Mg^{2+}-induced oxidative stress occurs, the endothelium may undergo chronic inflammation, characterized by increased activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), cytokines transcription and pro-inflammatory genes regulator [62]. On this basis, Mg^{2+} could be beneficial for G6PD deficient patients.

Zinc helps to maintain and develop both the innate and the adaptive immune system cells. *In vitro* studies showed that increased intracellular zinc concentration can damage the replication of some RNA viruses, including SARS-CoV-1 [5]. A meta-analysis based on 17 clinical trials involving a total of 2121 participants showed that zinc tablets may reduce the duration of common cold [53, 63].

Zinc mobilizes defense against ROS and H_2O_2-induced apoptosis, as an indirect antioxidant when administered prior H_2O_2 exposure, inducing expression of genes encoding antioxidant proteins (such as G6PD) *in vitro* [64]. Zinc has been proposed as a physiological signal to mediate oxidative stress response. Treatment with zinc and H_2O_2 at the same time has caused higher H_2O_2 toxicity than H_2O_2 alone, suggesting that zinc is a direct pro-oxidant in combination with H_2O_2 *in vitro* [64]. High zinc doses may be harmful on human health, because zinc can generate methemoglobin increase and oxidative stress via free radical in normal human erythrocytes, impaired immune and inflammatory responses (following an excess dose of 300 mg/day) and copper deficiency-related hemolytic anemia, because zinc may impair gastrointestinal copper absorption and inhibits G6PD activity, as observed in *in vitro* studies, leading to oxidative damage and consequent hemolytic anemia in G6PD deficient people [65].

Therapeutical dosage: copper 900 μg/day (maximum 10 mg/day) PO [52]; magnesium 1-40 g/day IV; zinc 30-200 mg/day PO [14, 53].

N-Acetylcysteine

N-Acetylcysteine (NAC) administration modulates redox system antioxidant effects, reduces brain copper-mediated oxidative stress and blocks CuI nanoparticle-mediated hydroxyl radicals and radical production *in vivo*. Moreover, NAC acts as an indirect antioxidant because increases manganese superoxide dismutase activity *in vivo*, thereby protecting cells from oxidative stress-mediated toxicity [57]. Lead-induced oxidative stress was attenuated by NAC treatment in erythrocytes *in vivo* increasing GSH levels, and *in vitro* facilitating ROS detoxification in G6PD deficient hu-

man erythrocytes, effects confirmed in a randomized controlled trial that demonstrated stimulation by NAC of GSH synthesis and erythrocyte G6PD activity in 122 healthy male workers taking 200-800 mg of NAC (out of 171 total individuals), more significantly compared with a control group [66]. As described in a case report, a treatment with three doses of 10 g over 24 h of IV NAC, followed by a single week discontinuation and one-week treatment with 600 mg every 12 h, was reported to give benefit to a G6PD-deficient 44-year-old male patient with severe COVID-19 infection, which had received a single dose of HCQ (400 mg). NAC caused hemolysis resolution, allowing removal from respirator and veno-venous extracorporeal membrane oxygenator until the full recovery. NAC may act via blockade of viral infection and the following cytokine storm [12]. Because of its antioxidant activity without reported hematologic adverse reactions so far, NAC could be beneficial for G6PD deficient people.

Therapeutical dosage: 600 mg/day PO [14].

Vitamins

Vitamin A has anti-oxidant properties and exerts a role in immune response and vision function. Several clinical trials show that vitamin A supplementation reduce morbidity and mortality with infectious diseases such as human immunodeficiency virus infection and malaria, and may protect against infections and their complications in 687 children aged 6-60 months [5]. Because of its antioxidant activity without reported hematologic adverse reactions so far, vitamin A could be beneficial for G6PD deficient people.

Since *B-complex vitamins* deficiency may weaken host immune response, supplementation could enhance virus-infected patients' immune system, also for COVID-19 treatment [5]. *Thiamine (Vitamin B1)* exerts anti-inflammatory and anti-oxidative roles, firstly by suppressing the oxidative stress-induced NF-kB activation, and has been proposed for restoring microvascular function in COVID-19 patients [28]. *Vitamin B12* modulates gut microbiota, which contributes to the development and function of both innate and adaptive immune systems, potentially preventing excessive immune reaction: a prospective study on microbiome data of 36 individuals showed persistent alterations in the fecal microbiome during the time of hospitalization in all 15 COVID-19 patients, compared with controls [61]. In an *in vitro* study, which examined the hemolytic effect of some B-complex vitamins (*niacin B5, pyridoxine B6*, thiamine) and *ascorbic acid (vitamin C)* on erythrocytes, vitamin C appeared to interact with erythrocytes and produce subsequent cell membrane lipid peroxidation and hemoglobin oxidation (Fe^{+2} to Fe^{+3}), at high concentrations (low concentrations have an antioxidant effect), mechanism also observed with the other vitamins; furthermore, vitamin B1 was the weakest hemolytic agent while vitamin C was the strongest one, compared with the other vitamins [66]. *Folic acid (vitamin B9)* contains the sub-component para-aminobenzoic acid, which is administrable to G6PD deficient people at therapeutic dosage [6].

Vitamin C might prevent the susceptibility to lower respiratory tract infections, such as those provoked by SARS-CoV-2, as suggested by results from three human controlled trials: lower incidence of pneumonia was observed in vitamin C-supplemented groups [5]. Vitamin C contributes to cytokine storm downregulation and *in vitro* studies showed vitamin C-driven protection of endothelium from oxidant injury [28]. Before taking *vitamin C (ascorbic acid)* is recommended to seek medical attention [14]. In 26 healthy volunteers, no change was observed in several markers of oxidative stress (e.g., DNA base oxidation products) after a single dose of 2g PO, whereas other studies reported a lower vascular stiffness augmentation index after acute vitamin C administration (e. g. a placebo-controlled randomized study involving healthy male volunteers) [68]. Noteworthy, high doses of vitamin C may act as pro-oxidant but only at high doses may prevent interaction between superoxide and nitric oxide. Moreover, higher vitamin C levels were associated with lower inflammatory markers levels, an effect confirmed also by the protective effect on erythrocytes only at supraphysiological concentrations. Vitamin C is oxidized to dehydroascorbic acid by ROS and reduced in cycle by GSH. Low concentrations would not be enough to interact with the great number of free radicals generated by pro-oxidant agents [69]. Several case reports showed acute hemolysis in G6PD deficient patients following administration of more than 40 g/day vitamin C (e. g. a 68-year-old black male who died after administration of 80 g IV for burns) [69] and very rare hemolytic anemia following high dose intake [14]. As there are little clinical evidence against vitamin C use in G6PD deficient patients, they can take it at therapeutic doses [69], e. g. as reported in a case report about a 30-year-old man with G6PD deficiency [8], such as 1-6 g/day, as used in MATH+ Protocol (Table 3), a dosage that may not be considered contraindicated in G6PD deficient patients according to *in vitro* studies and case reports [28, 70].

Vitamin D supplementation has been proposed in order to reduce the risk of influenza but observational studies and clinical trials results are contradictory. Vitamin D deficiency has been found to contribute to acute respiratory distress syndrome [53]. *In vivo* studies showed association between bovine Coronavirus infection and vitamins D and E decrease [5].

ROS overproduction may be the responsible of COVID-19-related impaired immunity, cytokine storm and pulmonary dysfunction. G6PD is necessary to prevent depletion of cellular GSH, required to maintain also the *Vitamin D*-metabolism genes and circulating levels of 25-hydroxyvitamin D (25(OH)VD). G6PD deficient people may be more susceptible to excess oxidative stress and 25(OH)Vitamin D deficiency, without the physiological defense systems for dealing with COVID-19 insults. Since genetic G6PD deficiency is common in the African American population and acquired deficiency of G6PD has been reported in obesity and diabetes in *in vitro* studies, vitamin D administration may reduce the COVID-19-related adverse clinical effects in those populations [71].

Animal and clinical studies have showed that *vitamin E* deficiency impairs both humoral and cell-mediated immune functions. The elderly people are predisposed to infections because of increased oxidative stress, inflammation and

immune system dysregulation, observations that suggest potential benefits of vitamin E supplementation on immune function, resistance to infection, infection-induced morbidity, especially in these patients most at risk in COVID-19 [53]. *Vitamin E* has antioxidant properties as it reduces oxidative stress through binding to free radicals, protecting cells from lysis, and a shortened erythrocyte survival was demonstrated in animal models with vitamin E deficiency [5, 69]. Several studies showed that high doses of vitamin E may reduce hemolysis rate in G6PD deficient people (e. g. one trial involving 68 G6PD deficient patients out of 102 subjects aged 5-40 years and another trial involving 36 male children carrying G6PD deficiency with mild chronic hemolysis), whereas other studies showed unchanged hematological status (*in vitro* and *in vivo* studies). Vitamin E exerts a role on chronic hemolysis in G6PD deficient people, however no adverse effect occurred following vitamin E oral administration between 400 IU to 2400 IU daily (safe up to 800 IU/day) [69].

Therapeutical dosage: vitamin A 100 000 UI/day PO; vitamin B1 50-100 mg/day IM; vitamin B9 5-15 mg/day PO; vitamin D3 750-2000 UI/day PO; vitamin E 400 mg/day PO; vitamin C 1 g/day PO [14].

DISCUSSION

The COVID-19 pandemic has led researchers and clinicians worldwide to discover and develop or repurpose drugs and therapies, in a profound effort to treat or at least contain the related symptoms (hyper-immune response, lung, gastrointestinal and renal damage mostly) and avoid a patients' worse outcome [1, 61]. The most mentioned drugs and nutraceuticals have been reviewed in order to provide a concise list of relevant studies and information and to make a critical evaluation on their safety in people with G6PD deficiency, resumed in the Table 1.

On the basis of this extensive literature search, the least safe drugs seem to be methylene blue, CQ, HCQ and ozone, which have shown different levels of safety and contradictory results: first of all, clinical studies regarding ozone on G6PD patients have not been found; regarding the first three drugs, the clinical studies performed to date show a low statistical significance, especially because of small sample size (often <30 recruited people), such as case reports; besides, clinical studies often involve people with unknown G6PD deficiency Class or with Class III (severe-to-moderate) G6PD deficiency, which undergo less severe symptoms related to oxidative stress, a choice that, excluding patients carrying Class I (severe) or II (very severe) G6PD deficiency, leads to publish less reports about more severe outcomes and to underrate the risk for this patients' subset. However, although their low statistical significance, most adverse events reported here had very high clinical significance (such as acute hemolytic crises) despite a lesser severity of G6PD deficiency in those patients, as they required hospitalization or resulted fatal. Furthermore, even in those cases treated successfully, it is needful to remind that, especially in situations of hospital overload (e. g. during the COVID-19 pandemic), a quicker and more effective first aid may represent the salvation for every single patient: avoiding use of unsafe therapies in G6PD deficient patients may contribute not only to save and address them towards a faster recovery, but also to shorten their hospitalization time and accordingly to care for a higher number of other patients' subsets.

The remaining reviewed COVID-19 drugs seem to be reasonably safe for G6PD deficient patients at therapeutic dosage, since none or only minor adverse events have been reported so far. Caution should be used especially for antibiotics, antivirals (excluding remdesivir), corticosteroids, deferoxamine, famotidine, interferons, monoclonal antibodies (excluding anakinra and emapalumab), NSAIDs, statins, minerals (excluding magnesium), vitamin C, which provoked minor adverse events; their administration should always be made under medical supervision. Since only pharmacovigilance reports were found about Angiotensin-Converting Enzyme inhibitors/Angiotensin II receptor blockers about their adverse effects on G6PD deficient people, more studies are needed in order to establish a rigorous safety evaluation.

Nevertheless, many therapeutical protocols provide for cocktails of drugs and nutraceuticals, safe when administered alone but potentially unsafe when mixed, since their adverse effects may be additive: more awareness about these low-risk drugs could improve G6PD deficient patients' outcome by developing and using alternative therapeutical protocols.

As stated in the Section 2, the search retrieved only a few clinical trials about COVID-19 and interactions with G6PD deficiency: two case reports [10, 12] and one phase III placebo-controlled randomized clinical trial (IRCT20200509047364N2) currently ongoing, which aims to investigate the effect of famotidine on the COVID-19 patients' recovery process and involves 20 patients [11], including some with G6PD deficiency. Noteworthy, G6PD deficiency is often considered an exclusion criterion for candidates' recruitment in clinical trials, e. g. in the COVERAGE randomized trial, which aims to evaluate several experimental treatments in patients aged ≥ 65 years with recent symptomatic COVID-19 [72], a choice that does not allow either detect or evaluate drug safety in G6PD deficient people.

This paper is not intended either to replace professional medical advice, diagnosis or treatment, which is dependent on individual medical evaluation, or to give therapy guidelines, but aims to provide a guide for avoiding administration of dangerous drugs or nutraceuticals where possible, collecting and reporting any scientific documentation that may be usefully brought to the healthcare personnel's and patients' awareness. Both screening for G6PD deficiency and check for dangerous drugs and their excipients before administration appear necessary in order to avoid drug-associated adverse reactions (e.g., excessive oxidative stress, anemia and rhabdomyolysis) in those who are unaware of their status.

The knowledge gap in safety of COVID-19 therapies in G6PD deficient people should be filled with more research about pharmacogenomic literature available for COVID-19 drug therapies, in order to find and analyze genetic markers and variants with possible implications in response to therapies, as recently performed as far as regards G6PD deficiency and CQ/HCQ [73, 13], about drug biochemical pathways and risks in this patients' subset compared with the

general population, to better evaluate their safety and possible alternatives.

CONCLUSION

On the basis on the examined scientific literature, the drugs to be avoided into G6PD deficient patients are methylene blue, CQ, HCQ and ozone, because of their oxidant potential that may trigger hemolysis (clinically confirmed for the first three drugs). The other reviewed drugs and nutraceuticals seem to be less or not dangerous for G6PD deficient patients but, however, should be administered at therapeutic doses under medical supervision. Caution may allow you to avoid or, at least, manage any drug-associated symptoms such as hemolytic crisis, which can impair G6PD deficient patients' clinical outcome, especially if also carrying infectious disease such as COVID-19, capable of enhancing inflammation and oxidative stress inside the organism.

AUTHORS' CONTRIBUTIONS

Carmela Iosco: Conceptualization, Literature Search, Writing- Original draft preparation, Visualization, Supervision. **Verity Eason:** Literature Search, Writing- Review & Editing. **Ibrahima Gueye:** Literature Search, Writing- Review & Editing. **Renee Leavy:** Literature Search, Writing- Review & Editing.

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All the authors are members of Global G6PD Deficiency Task Force, an international network that connects volunteer specialists and committed people to raise awareness about this condition.

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ETHICAL ISSUES

Availability of Data and Material

Not applicable.

Code availability

Not applicable.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Submission

The work described has not been published previously, is not under consideration for publication elsewhere, its publication is approved by all authors. If accepted, the work will not be published elsewhere in the same form, in English or in any other language.

COVID-19 drugs and glucose-6-phosphate dehydrogenase deficiency: a matter of life threatening and public health

LIST OF ABBREVIATIONS

COVID-19 Coronavirus disease 2019
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
G6PD Glucose-6-phosphate-dehydrogenase
NADPH Nicotinamide adenine dinucleotide phosphate
GSSG oxidized glutathione
GSH reduced glutathione
ROS reactive oxygen species
PO *per os*
IV intravenous
IM intramuscular
STAT1 Signal transducer and activator of transcription 1
IFIT3 Interferon induced protein with tetratricopeptide repeats 3
OAS1 2'-5'-Oligoadenylate Synthetase 1
TRIM22 Tripartite Motif Containing 22
PI-3K Phosphoinositide 3-kinase
MTOR Mammalian target of rapamycin
LTV/RTV Lopinavir/Ritonavir
IFN Interferon
SC Subcutaneous
CQ Chloroquine
HCQ Hydroxychloroquine
BID *bis in dīe* (twice/day)
JAK Janus kinase
NSAIDs Non-steroidal anti-inflammatory drugs
ATP Adenosine triphosphate
PO_2 Partial pressure of oxygen
CoQ10 Coenzyme Q10
CYP450 Cytochrome P450
ALA Alpha-Lipoic Acid
NOS Nitric oxide synthase

NF-kB nuclear factor kappa-light-chain-enhancer of activated B cells
NAC N-Acetylcysteine

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