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*Mini review article*

# THE ROLE OF DISTURBED REDOX HOMEOSTASIS IN COVID-19

# ULOGA NARUŠENE REDOKS HOMEOSTAZE U COVID-19

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## Abstract

Coronavirus disease (COVID-19) is an acute respiratory disease caused by the SARS-CoV-2 that has spread throughout the world, causing millions of deaths. COVID-19 is characterized by the interplay of inflammation and oxidative stress, which may be one of the main mechanisms by which SARS-CoV-2 infection leads to severe acute respiratory failure. Main components of enzymatic antioxidant protection are: superoxide dismutase (SOD), glutathione peroxidase (GPX) and glutathione transferase (GST). A transcription factor that controls the basal activity and coordinated gene expression of specific antioxidant enzymes (Nrf2) is one of the most significant regulatory antioxidant proteins. The activity and antioxidant enzymes and regulatory protein expression are influenced by the polymorphism of the genes that encode them. In this review, the role of disturbed redox homeostasis and antioxidant gene profile in COVID-19 susceptibility were acknowledged, as well as disease severity.

**Keywords:**
COVID-19,
SARS-CoV-2,
redox homeostasis,
gene polymorphisms
antioxidant profile

## Sažetak

Koronavirusna bolest (COVID-19) akutna je respiratorna bolest uzrokovana koronavirusom SARS-CoV-2 koja se proširila širom sveta izazivajući milione smrtnih slučajeva. Karakteriše je prisustvo inflamacije i oksidativnog stresa, koji igra jednu od ključnih uloga u razvoju teške akutne respiratorne insuficijencije izazvane infekcijom SARS-CoV-2. Glavne komponente enzimske antioksidativne zaštite su: superoksid dizmutaza (SOD), glutation peroksidaza (GPX) i glutation transferaza (GST). Jedan od najvažnijih regulatornih antioksidativnih proteina je Nrf2, transkripcioni faktor koji reguliše bazalnu aktivnost i koordinisanu ekspresiju gena za prethodno navedene antioksidativne enzime. Na aktivnost antioksidativnih enzima i regulatornih proteina utiču polimorfizmi gena koji ih kodiraju. U ovom preglednom članku pokušali smo da istaknemo ulogu poremećene redoks homeostaze i antioksidativnog genetskog profila u podložnosti za nastanak i progresiju COVID-19.

**Ključne reči:**
COVID-19,
SARS-CoV-2,
redoks homeostaza,
genski polimorfizmi,
antioksidativni profil



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## Introduction

### Means of antioxidative defence

Oxidative stress is involved in numerous infectious and non-infectious diseases (1). This state of impaired redox homeostasis is caused by an increased production of free radicals followed by inadequate antioxidant protection (2-4). Increased free radical levels damage biologically important macromolecules, causing breaks in DNA strands, lipid peroxidation, and degradation of proteins. Therefore, impaired balance between oxidative stress and defence and/or reparative mechanisms can lead to cell damage and activate stressogenic response and pro-inflammatory cascades (4). To prevent oxidative damage to biologically significant macromolecules, the human body has evolved many enzymatic and non-enzymatic antioxidant defence systems against free radicals (5). Superoxide dismutase (SOD) isoenzymes are the immediate line of defence against free radicals, and glutathione peroxidase (GPX) and glutathione transferase (GST) isoenzymes are the first line of enzymatic antioxidant protection (**Figure 1**). Regulatory antioxidant protein Nrf2 (Nuclear factor-erythroid-2-related factor 2) is a transcription factor that controls the basal activity and coordinated gene expression of several important antioxidant enzymes. The expression and activity of both catalytic and regulatory antioxidant proteins are influenced by the polymorphism of genes that encode them. It is considered one of the key factors during the response to oxidative stress. It stimulates the transcription of genes related to drug metabolism, antioxidant defence, signal transduction, and, to a lesser degree, cell replication, metabolism, and proteasomal activity (6). Therefore, adequate expression of Nrf2 in cells affects its ability to facilitate a timely response to oxidative, inflammatory, and metabolic stress (7). The promoter region of Nrf2 contains the most significant functional polymorphism, Rs6721961 (-617C/A), which decreases Nrf-2-dependent gene transcription (8). Certain genes of

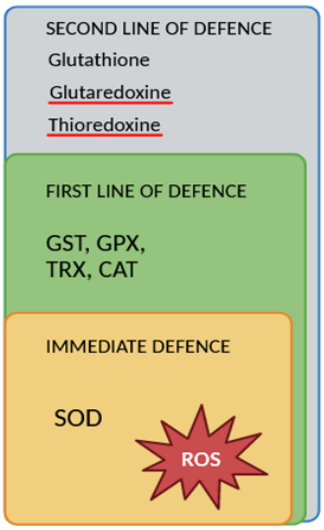


**Figure 1.** Levels of antioxidative defence

ROS – Reactive oxygen species, SOD - Superoxide dismutase, GST – Glutathione S transferase, GPX – Glutathione peroxidase, TRX – Thioredoxin, CAT – Catalase

cytosolic GSTs classes, such as GSTA1, GSTM1, GSTM3 and GSTP1, are among Nrf2 targets. Glutathione transferase polymorphisms are common in the human population, ranging from 20 - 60% (9). Deletion polymorphisms within the *GSTM1* and *GSTT1* classes affect the availability of enzymes, so in homozygous carriers for the null allele of these genes, GSTM1 and GSTT1 enzymes are completely absent (10). Numerous single-nucleotide polymorphisms (SNP) of different GST classes (*GSTP1* (AB) Rs1695, *GSTP1* (CD) Rs1138272, *GSTO1* Rs4925, *GSTO2* Rs156697, *GSTM3* Rs1332018) also affect the expression and activity of these enzymes (10,11). In case of *GSTP1* SNP (AB) Rs1695 polymorphism, the A313G substitution causes replacement of isoleucine with valine at position 105 (Ile105Val), while at SNP (CD) Rs1138272 the existence of thymine instead of cytosine at position 341 results in replacement of alanine with valine (Ala114Val), and the variants of both SNPs affect the affinity of *GSTP1* towards the substrate (8). The *GSTP1*ABCD haplotype represents a combination of these two polymorphisms. In both *GSTO* genes, *GSTO1* and *GSTO2*, two functional polymorphisms were most often studied: *GSTO1* Ala140Asp (Rs4925) and *GSTO2* Asn142Asp (Rs156697). The *GSTO1* SNP is at nucleotide position 419, causing an amino acid substitution of alanine to aspartate at AK position 140 (Ala140Asp) of exon 4. The *GSTO2* Rs156697 SNP is characterized by a substitution at nucleotide position 424 and causes an amino acid substitution of asparagine to aspartate at AK position 142 (Asn142Asp) of exon 4 (9). It was shown that the *GSTO1* Rs4925 polymorphism primarily causes a change in the deglutathionylase activity of GSTO1. On the other hand, the variant *GSTO2*G* allele leads to lower expression of the *GSTO2* gene (9). A SNP within the *GSTM3* (Rs1332018, A-63C) gene is located in the promoter region of the transcription factor binding site, indicating its potential regulatory significance (8). Therefore, *GSTM3* variant genotype carriers show reduced *GSTM3* expression, due to weaker binding of RNA polymerase II (8).

The SOD2 isoenzyme is located in mitochondria and converts superoxide anion into hydrogen peroxide, providing immediate enzymatic antioxidant protection against reactive oxygen species (ROS). Within *SOD2*, gene Rs4880 SNP has gained lots of attention. This SNP causes a substitution of the amino acid valine with alanine, which reduces the efficiency of SOD2 transport into mitochondria by 30 - 40% and thus leads to a reduced potential for superoxide anion neutralization (8). Since GPX is the primary enzyme in the process of further neutralizing ROS, it eliminates soluble hydrogen peroxide. Also, GPX1 is present in the cytosol and mitochondria of all cells, while GPX3 isoenzyme is mainly present in plasma. Furthermore, *GPX1* Rs1050450 SNP entails a cytosine-thymine substitution that is associated with reduced GPX1 isozyme activity (8). The downregulation of gene transcription caused by a polymorphism in the *GPX3* gene (rs8177412) results in a considerably lower GPX3 plasma activity (12).

## Disturbance of redox homeostasis in SARS CoV-2 infection

Dysregulation of the host antioxidant mechanisms has a significant part in the evolutionary process of various viral diseases, including COVID-19 (13). Numerous data points to a connection between COVID-19 pathology and particular biological responses, like oxidative stress and inflammation. It is believed that oxidative stress in COVID-19 has a number of roles in several processes, such as the virus's interaction with host cells, replication, and maintenance of an augmented inflammatory response (14, 15). A prooxidant milieu is necessary for SARS-CoV-2 entry into host cells because the host's ACE2 receptor has to keep its disulfide bonds intact in order to connect with the spike glycoproteins that are rich in cysteine (16). Once within the host cell, the virus uses the cell's machinery to replicate itself, which throws off the oxidative balance and increases the creation of harmful ROS and mitochondrial dysfunction. Moreover, clinical evidence suggests that oxidative stress and worsened redox status in COVID-19 patients could potentially contribute to the progression of the disease (13, 18). In addition, the role of oxidative stress has been recognized during the COVID-19 disease in enhancing and maintaining the cytokine storm, coagulopathy and cell hypoxia (18). A characteristic of COVID-19 is that it causes an uncontrollably high level of inflammation called as a "cytokine storm", which is linked to the severity of the illness and mortality risk (12, 15). Patients infected with SARS-CoV-2 virus release a lot of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α and interferon-ϒ (IFN-ϒ), which induce ROS production and oxidative stress (20). However, ROS behave as signalling molecules that, in a positive feedback loop, encourage the creation of pro-inflammatory cytokines. This vicious cycle is crucial to the development of inflammation and increases the likelihood that the host will suffer a severe course of the disease (16, 17). Furthermore, excessive ROS production is associated with T and B immune cells development and differentiation. The redox microenvironment is widely recognized as a critical regulator of immune cell activation and proliferation (22). Specifically, increased oxidative status promotes Th1 cell activation, while enhanced reduced status causes Th2 response (23). In COVID-19 patients, severe inflammation and oxidative stress both contribute to the progression of the disease, damage cell structures, result in different kinds of tissue and organ damage, and increase the severity and fatality of the illness (24). On the other hand, pro-oxidative enzymes and the SARS-CoV-2 spike protein can directly activate oxidative stress pathways, or they can be activated indirectly by inducing an inflammatory cascade that in turn triggers oxidative stress pathways through inflammasome activation. (25). Disruption of redox homeostasis and inflammation also induces endothelial dysfunction, another important pathophysiological mechanism in COVID-19 patients (26). In numerous organs, mainly the lungs, oxidative stress and cytokine storm cause endothelial cells to undergo ROS-dependent apoptosis, which results in the release of coagulation factors and the development of blood clots (27,28). As mentioned, IL-1β and IL-2 are known generators of ROS and reactive nitrogen species (RNS) production, while IL-6 activates monocytes and neutrophils, which further increases the generation of ROS (29). Patients with severe COVID-19 typically have elevated neutrophil counts, and a high neutrophil/lymphocyte ratio during the early stages of the disease is predictive of a poor prognosis. Additionally, high levels of IL-6 are linked to a higher death rate in patients receiving intensive care (30). Few studies, as well as experimental models of acute respiratory distress syndrome (ARDS), suggested that oxidative stress and innate immunity are one of the main pathways of lung damage that affect the severity of acute lung injury and development of ARDS, which is the leading cause of death in COVID-19 patients (29, 30, 34) (**Figure 2**). Glutathione (GSH) functions as a major cellular antioxidant and is involved in different processes, including antiviral protection and immune system response (32). Specifically, GSH may avert COVID-19 cytokine storm by blocking the NF-kB pathway and lowering free radical levels (33). Furthermore, through controlling cellular redox and thiol homeostasis,

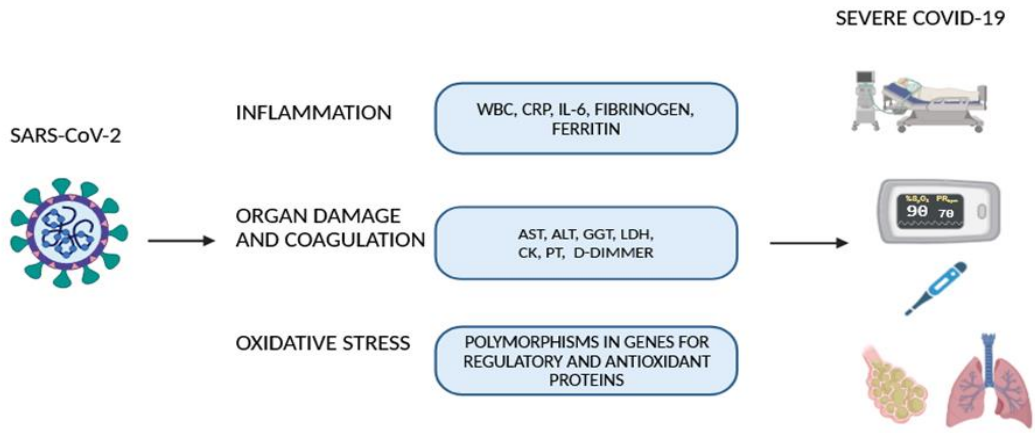


**Figure 2.** SARS-CoV-2 infection features

WBC – White blood cells, CRP – C-reactive protein, IL-6 – interleukin 6, AST – aspartate transferase, ALT – alanine transferase, GGT – gama-glutamate transferase, LDH – lactate dehydrogenase, CK – creatine kinase, PT – prothrombin time

a number of antioxidant drugs, including GSH, may lessen the interaction of SARS-CoV-2 with ACE 2 host receptors (34). This could provide a reasonable explanation for the correlation between lower GSH levels and a higher likelihood of developing the severe type of COVID-19. According to a number of studies, oxidative stress markers are elevated in COVID-19 patients when compared to healthy controls, as well as in severe cases of the disease when compared to less severe cases and controls. Namely, the levels of markers of lipid oxidative damage, assessed as concentration of malondialdehyde (MDA) were the highest in COVID patients treated in intensive care units (ICU) as opposed to outpatients and controlled healthy subjects (35-38). Timely trend of MDA concentration was noticed over the course of the disease in COVID patients with no previous comorbidities associated with disturbed redox homeostasis. Such background provided the opportunity of assessing the interplay of oxidative stress and inflammation by analysing the significance of neutrophil induced oxidative stress in COVID patients, as the levels of DNA oxidative damage markers correlated with the increase of absolute neutrophil number (15, 39, 40). Oxidative damage of proteins can be assessed as the consumption of thiol groups within proteins, however, some studies were measuring the level of advanced oxidation protein products (AOPP) as indicators of monocyte mediators, serving as possible indirect markers of previously mentioned interaction of inflammation and oxidative stress (41). The study of Ducastel et al. showed that the level of AOPP was connected with the degree of COVID 19 severity and therefore the urge for ICU treatment and eventually mortality (42). Reduced levels of thiols and total antioxidant capacity were registered in patients with COVID-19 and were associated with the severity of the clinical presentation and worse outcome (43, 44).

## The polymorphism of regulatory and catalytic antioxidant proteins in COVID-19

Although viral infections are accompanied with ROS production, antioxidant enzymatic defence seems to be quite strenuous (45). The baseline level of antioxidant defence is insufficient to completely neutralize the harmful effects of ROS, because of the severe inflammatory state and excessive generation of extracellular and intracellular free radicals. Thus, antioxidant-based therapies might help manage infectious diseases by decreasing oxidative stress and, as a result, enhancing host immune responses. During viral infections, Nrf2 activation has a cytoprotective effect (Zika, Ebola and Influenza A viruses (IV), SARS CoV2) and also, all diseases where poorly controlled inflammation has a pathogenetic role (46). It is believed that some IV strains increase Nrf2 translocation and transcription, hence activating the Nrf2/ARE defence mechanism (47). In contrast to IV, the human respiratory syncytial virus reduces the amounts of Nrf2 and mRNA in the airway epithelial cells' nucleus (47, 48). Several studies are reporting that Nrf2 plays a role in suppressing the upregulation of pro-inflammatory cytokines (47, 49). In addition to preventing tissue and cell damage, Nrf2 also lowers the production of damage-associated molecular pattern proteins (DAMPs), which are generated by necrotic cells and have a crucial immunological role in enhancing the inflammatory response (50-52). One of the major regulators of redox homeostasis, the thioredoxin system, which consists of nicotinamide adenine dinucleotide phosphate (NADPH), thioredoxin reductase (TRXR), and thioredoxin (TRX), is also mediated by Nrf2. Consequently, TRXR converts oxidized TRX into active reduced TRX at the expense of NADPH (53). By promoting the production of TRXR and activating TRX, which in turn breaks down the disulphide bonds between SARS-CoV-2 and ACE2, Nrf2 activation could mitigate oxidative stress and stop COVID-19 progression (54).

There is mounting evidence linking COVID-19 to Nrf2 suppression. Multiple studies have revealed that COVID-19 patients had lower Nrf2 expression (55, 56). According to Gümüs et al., children with COVID-19 had greater levels of oxidative stress index and total oxidative state status, as well as lower mean Nrf2 expression values and total antioxidant levels than the control group. Total oxidative stress (TOS) and oxidative stress index (OSI) were shown to have a substantial negative connection with Nrf2, and the TOS and OSI values were found to significantly decrease as the Nrf2 levels increased (56).

Concerning GST, there are some studies that implicated that polymorphism of different GST genes is connected to the onset and intensity of COVID-19. Namely, individuals with the *GSTT1*-null genotype have a positive connection with COVID-19 mortality, as demonstrated by Sadat and colleagues (57). One of the more significant consequences of COVID-19 is lung fibrosis, which is linked to *GSTT1* and *GSTM1*-null genotypes in patients with chronic obstructive pulmonary disease, according to an interesting study by Ding et al. (58). According to one study, patients with severe COVID-19 had higher frequencies of null alleles *GSTM1-/-* and *GSTT1-/-* than patients with milder clinical symptoms. Additionally, patients with the *GSTT1-/-* genotype had a higher mortality rate than those with the *GSTT1+/1* genotype (59). Ćorić et al. proved an association between two *GSTP1* (Rs113272, and Rs1695) and *GSTM3* polymorphisms and COVID-19 susceptibility and severity (10). Namely, this study reported that individuals with at least one *GSTP1** Val allele (Rs113272) were less likely to get COVID-19 compared to *GSTP1* AlaAla wild genotype. In case of *GSTM3* (Rs1332018, A-63C) polymorphism, a lower chance of developing COVID-19 was found in carriers of the *GSTM3* AC genotype compared to the *GSTM3* AA. The same study concluded that individuals with the GSTP1 (Rs1695) IleVal genotype have almost 3-fold lower risk of developing COVID-19, compared to carriers of the wild-type *GSTP1* IleIle genotype. Since those with more risk genotypes are more likely to contract COVID-19, this study also demonstrated the cumulative influence of GST gene polymorphisms on the

disease's development. That is to say, those who carry any one of the three risk genotypes - *GSTP1**Ile, *GSTP1**Ala, or *GSTM3**C -have a fourfold increased risk of contracting a severe case of COVID-19 (10).

According to Đukić and colleagues' study on the relationship between *GSTO1* and *GSTO2* polymorphisms and COVID-19 in the Serbian population, carriers of the *GSTO1**AA and *GSTO2**GG polymorphisms have a higher risk of contracting the virus than carriers of the *GSTO1* and *GSTO2* wild type (11). This study included haplotype analysis, which revealed that carriers of H2 haplotypes, which included the variant alleles for *GSTO1**A and *GSTO2**G, had a 2-fold increased risk of contracting COVID-19 (11).

Antioxidant genetic profile may enable quick identification of more prone individuals and their timely treatment. So far, antioxidants such as glutathione and its precursor N-acetyl-cysteine, as well as vitamin C, seem promising as a novel treatment approach for "cytokine storm syndrome" and respiratory distress in patients with COVID-19 pneumonia (60,61). Still, not all patients received this type of treatment. It seems biologically plausible that individuals with genetically predetermined lower antioxidant defence systems might be considered as candidates for this type of treatment if timely recognized.

Some studies measured serum activity of SOD and GPX in COVID-19 patients. Despite elevated levels of CAT and SOD in patients with COVID-19, elevated levels of ROS were also detected, which were associated with disease severity (62). According to one study, patients with SARS-CoV-2 infection had higher GPX activity than controls. The same study showed higher serum activity of SOD and total antioxidant capacity concentration (TAC) in COVID-19 patients compared to controls (63). Golabi et al. did a study, where it was registered that COVID-19 patients treated on an outpatient basis had higher values of SOD and GPX compared to controls (63). The latest study of Tavassolifar et al. from 2023. reported that the SOD and CAT expression and activity were increased in the PBMCs and plasma of patients with COVID-19 (64). However, in contrast to controls, other investigations found that individuals with COVID-19 had lower plasma erythrocyte GSH, GPX, CAT, and SOD levels. (65). In the study conducted by Jerotić et al., a significant association for COVID-19 development was found for *GPX3* Rs8177412 polymorphism. The risk of developing COVID-19 was notably reduced between carriers of the *GPX3**TC + CC genotype in contrast to carriers of the *GPX3**TT genotype. In addition, Jerotic et al. reported that *SOD2* Rs4880 and GPX1 Rs1050450 polymorphisms influence the biochemical profile of COVID-19 patients. Specifically, greater levels of fibrinogen and ferritin were substantially associated with the *SOD2**Val allele, whereas higher levels of fibrinogen and d-dimer were associated with the *GPX1**Leu allele (8).

## Conclusion

The development and progression of COVID-19 are intimately linked to oxidative stress and inflammation.SARS-COV-2 disrupts the redox balance of the host both intracellularly and extracellularly, which results in immunological dysregulation and the emergence of a severe form of the illness. In COVID-19 patients, the genetic profile of antioxidant enzymes may also be highly significant in determining risk assessment, illness severity, and prognosis. Determining genetic susceptibility biomarkers simultaneously may improve the definition of a person's unique redox profile and potentially allow prompt COVID prevention and effective personalized therapy. Namely, in future era of precision medicine, specific antioxidant genetic profiling may provide a medical model that proposes the customization of healthcare, with accurate medical decisions and specific antioxidant treatments, being tailored to the individual patient.

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