European Review for Medical and Pharmacological Sciences 2023; 27: 6459-6471

Oxidative stress and inflammation in COVID-19: potential application OF GLP-1 receptor agonists

R.A. ABUDALO[1], A.M. ALQUDAH[1], C. ROARTY[2], R.Y. ATHAMNEH[3], D.J. GRIEVE[2]

[1]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmaceutical Sciences, The Hashemite University, Zarqa, Zarqa, Jordan
[2]Wellcome-Wolfson-Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK
[3]Faculty of Allied Medical Sciences, Zarqa University, Zarqa, Jordan

Abstract. **COVID-19 is a global pandemic with devastating economic and public health impacts, which is particularly associated with increased incidence of respiratory and cardiovascular disease together with inflammation and oxidative stress as essential underlying features. Glucagon-Like Peptide-1 (GLP-1) receptor agonists are now routinely used for the clinical management of type 2 diabetes due to their established glucose-dependent insulinotropic actions. However, these agents also display a variety of pleiotropic functions, including the promotion of anti-inflammatory and antioxidant responses, highlighting likely therapeutic applications beyond glycemic control. Given that COVID-19 is particularly linked with adverse modulation of inflammatory and oxidative signaling, which are known to be impacted by GLP-1 receptor activation, it seems logical that GLP-1 receptor agonists may be beneficial for the clinical management of patients with SARS-CoV-2 infection. In this review, we discuss the specific role of inflammation and oxidative stress associated with COVID-19, including underlying pathogenic mechanisms, as the basis for the potential therapeutic application of GLP-1 receptor agonists to combat both acute and chronic complications of this devastating disease.**

Key Words:
Glucagon-like peptide-1, SARS-CoV-2, COVID-19, Inflammation, Oxidative stress.

Introduction

The 2019 coronavirus disease (COVID-19) first appeared in late December 2019 in Wuhan City, Hubei Province, among individuals who were diagnosed with pneumonia of unknown cause, and widespread throughout China by 30 January 2020[1]. The World Health Organization subsequently classified COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as a global pandemic on 11th March 2020, with the disease widespread and persistent in over 220 nations around the world[2,3]. Symptoms typically include fever, headache, dry cough, dyspnea, and disorientation, and can range from moderate to severe, including hypoxia and acute respiratory distress syndrome (ARDS), leading to death in extreme cases[4]. As of October 2022, >618 million global SARS-CoV-2 infections and >6.5 million COVID-19-related deaths were confirmed. Notably, whilst largely a respiratory condition, COVID-19 is linked with cardiovascular complications, with a significant proportion of deaths occurring due to chronic heart failure subsequent to SARS-CoV-2 infection[5,6].

Further to the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, SARS-CoV-2 is the third highly pathogenic and large-scale epidemic coronavirus to arise in the twenty-first century[7]. SARS-CoV-2 was named after its genetically related predecessor, SARS-CoV (now known as SARS-CoV-1), and contains sequences not previously detected in human or animal viruses[8,9]. Its structure comprises a protein envelope surrounding each SARS-CoV-2 virus particle, containing its single-stranded RNA genome, which encodes for four structural proteins: spike, membrane, envelope, and nucleocapsid proteins. Spike (S) protein interacts with the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of human airway epithelial cells, with spike protein primed by the transmembrane protease serine 2 (TMPRSS2) serine protease, permitting virus entry and replication *via* integration into the cell's RNA and protein synthesis machinery (Figure 1)[10].

It has been demonstrated that SARS-CoV-2 binds to ACE2 receptor-expressed cells (Figure 1)

Corresponding Author: Rawan A. Abudalo, Ph.D; e-mail: rawana@hu.edu.jo

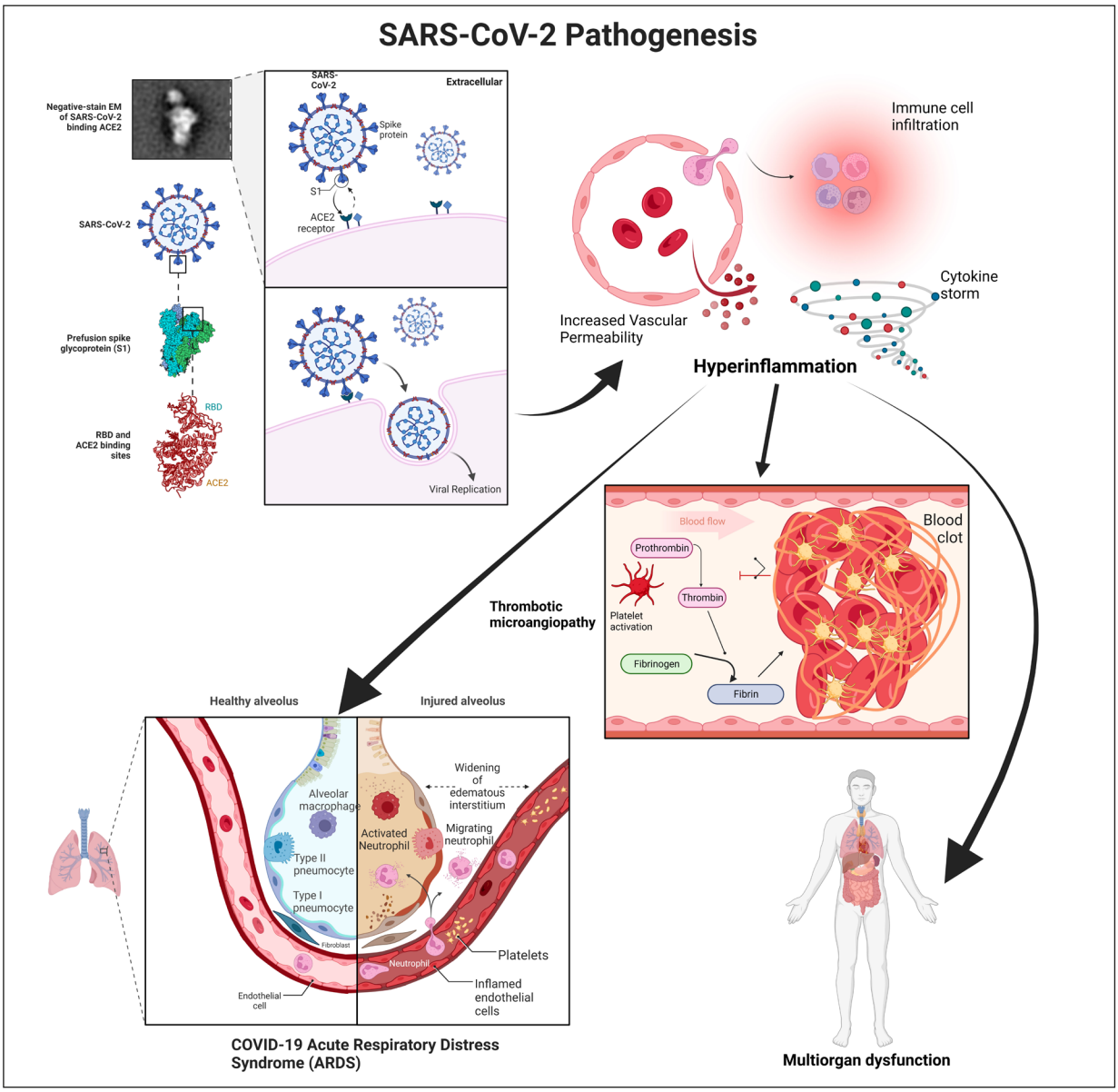

Figure 1. Pathogenesis of SARS-CoV-2 infection. Spike (S) protein binds to the ACE2 receptor on respiratory epithelial cells, facilitating virus entry, replication, and RNA integration, and promoting virus prevalence and persistence. The resultant cytokine storm leads to a hyperinflammatory state characterized by increased vascular permeability and immune cell infiltration, which may progress to thrombotic microangiopathy, acute respiratory distress syndrome (ARDS), and multiorgan dysfunction.

but not those cells without receptor expression[11]. The binding mechanism illustrated as the virus receptor binding domain presented in spike glycoprotein binds to ACE2 receptor mainly subdomain I[12], causing virus-host cell membrane fusion, which subsequently releases the viral RNA to the cytoplasm, therefore establishing infection state[13]. While some transmembrane proteinases, such as transmembrane protease serine 2 (TMPRSS2) and metallopeptidase domain 17 (ADAM17), or other proteins, such as vimentin, may be contributed to virus receptor binding and fusion[14]. For example, protease serine 2 TMPRSS2 transmembrane proteinase can promote virus uptake by cleaving ACE2[15].

Whilst angiotensin-converting enzyme (ACE), as a part of renin- the angiotensin system (RAS), plays a significant role in maintaining electrolytes hemostasis and controlling blood pressure through angiotensin 2 formation, causing vasoconstriction and salt retention[16]. In addition, when angiotensin

2 binds to the angiotensin type 1 receptor (AT1R), it causes cell proliferation, extracellular matrix remodeling, and inflammatory responses[17]. Although a homology between ACE and ACE2 is established, ACE2 counteracts the Mas receptor physiological effects of RAS by catalyzing the conversion of angiotensin II to angiotensin-(1-7) that binds to induce vasodilation, anti-inflammatory, and anti-fibrosis effects[18]. Thereby, the interaction between SARS-CoV-2 and ACE2 receptor causes angiotensin II/AT1R activation inducing fibrosis, inflammation, and oxidative stress. Meanwhile, it has been established that AT1R activation by angiotensin II promotes epithelial lung alveolar cell apoptosis[19], and endothelial cell dysfunction *via* generation of reactive oxygen species[20]. As well as the inflammatory mechanism of angiotensin II may involve nuclear factor (NF)-κB activation and interleukins as IL-6 transcription[21]. Therefore, SARS-CoV-2 induced immune system response in association with high angiotensin II level could promote the hyper-inflammatory state in infected patients.

The analysis of ACE2 protein expression has demonstrated that heart, lungs, kidney, colon, and small intestine are the tissues with the highest ACE2 expression, unlike blood cells[22], and the presence of SARS-CoV-2 in heart, lung, and renal tissues was confirmed by Scanning Electron microscope (SEM) and transmission electron microscope (TEM)[23]. This indicates that SARS-CoV-2 may attack different organs with high ACE2 receptor expression besides the lungs, which may cause multiple organ dysfunction such as acute renal injury, and acute cardiac injury in addition to acute lung injury[24].

Although precise mechanisms underlying COVID-19 pathophysiology are not defined, inflammation is established as a central feature, with abnormalities in immune cell profile and circulating inflammatory markers linked to disease severity and outcome[25]. Indeed, SARS-CoV-2 is typically associated with cytokine storm (also known as cytokine release syndrome), which is driven by pathogen-triggered inflammation and accentuated by a positive feedback loop[26] Cytokine storm specifically involves inappropriate activation of the innate immune response, cell death, and excessive inflammatory cytokine secretion[27,28], which is linked with increased severity of COVID-19 and mortality. Notably, immune dysregulation in COVID-19 is associated with oxidative stress, defined as an imbalance between oxidants and antioxidants, which plays a key role in viral pathogenesis[29] and has been linked with worsened outcomes in COVID-19 patients[30]. Indeed, oxidative stress in COVID-19 is specifically associated with the amplification and persistence of cytokine storm, coagulopathy, and cellular hypoxia[31], with considerable contributions from oxidative damage due to redox imbalance and iron dysregulation[32].

Over recent years, a new class of drugs known as glucagon-like peptide-1 receptor (GLP-1R) agonists have emerged as an effective treatment for type 2 diabetes mellitus (T2DM) and obesity[33]. GLP-1 is an incretin peptide hormone of 30 or 31 amino acids that are primarily released by three tissues in the human body: enteroendocrine L cells in the distal intestine, pancreatic alpha cells, and the central nervous system[34]. Whilst GLP-1R activations exert effective glycemic control in a glucose-dependent manner, it also regulates a variety of pathophysiological processes associated with inflammation, including thrombosis, fibrosis, and adverse tissue remodeling[35,36].

As a result, in addition to clinical management of metabolic disease, GLP-1R agonists, such as liraglutide and exenatide, show clear promise for the treatment of inflammatory disorders, particularly those linked with cardiovascular and renal disease[37]. Whilst the established metabolic effects of GLP-1R agonists make this pharmacological class the preferred option for treating many individuals with T2DM, its pleiotropic actions highlight potential additional benefits beyond glycemic control, which are likely to extend to SARS-CoV-2 infection[38]. Indeed, it was recently reported that pre-symptomatic use of GLP-1R agonists in T2DM patients was linked with decreased risk of severe disease and mortality after SARS-CoV-2 infection[39].

Given continuing high numbers of reported COVID-19 cases and deaths, specific treatment options are urgently needed in order to reduce poor acute and chronic outcomes. In this regard, it is evident that effective management of inflammation associated with SARS-CoV-2 infection and COVID-19 holds the potential to limit disease severity and consequences[25]. As such, this review article specifically focuses on the central role of inflammation and oxidative stress in COVID-19 pathogenesis and the emerging potential of GLP-1 signaling as a candidate therapeutic target.

Oxidative Stress in COVID-19

Reactive oxygen species (ROS) comprise free radicals and non-free radicals, which are derived from oxygen and exhibit intense chemical reactivity due to unpaired electrons. Specific ROS

include superoxide anions, hydrogen peroxide, hydroxyl radicals, ozone, and singlet oxygen[40], which are extremely reactive oxygen-containing molecules resulting from the inadequate cellular reduction of molecular oxygen[41]. Oxidative stress is defined as an imbalance between the generation of ROS within cells and tissues, and endogenous detoxification mechanisms, such as superoxide dismutase, catalase, and glutathione peroxidase[42,43]. Whilst ROS signaling is vital to support homeostasis, it has the potential to become dysregulated and detrimental to normal physiology[44]. Indeed, increased ROS levels are linked to oxidative damage of many cellular compartments and components, with ROS-related structural and functional abnormalities of membrane-associated macromolecules, such as lipids and proteins, identified in numerous tissues, including the brain[45].

Notably, ROS signaling is known to be particularly important in maintaining normal endothelial cell function and determining cardiovascular disease progression[46], whilst endothelial cells have emerged as significant drivers of inflammation associated with SARS-CoV-2 infection and COVID-19. Redox signaling within endothelial cells may be mediated by ROS derived from different sources, including xanthine oxidase, NOX NADPH oxidases, and dysfunctional nitric oxide synthase, but is predominantly determined by mitochondrial ROS (mtROS), which in excess quantities, promotes oxidative stress, inflammation, and chronic endothelial dysfunction[47]. Interestingly, SARS-CoV-2 infection appears to be associated with significant induction of oxidative stress genes in both immune and pulmonary cells *vs.* other respiratory viruses[48], with a ten-fold higher affinity for alveolar cells compared to SARS-CoV-1. It is conceivable that disruption of normal gene expression due to free radical generation and subsequent oxidative stress may impact cellular replication of SARS-CoV-2 further to entry *via* the ACE2 receptor, radically changing virus structure[49]. Similar to other coronaviruses, SARS-CoV-2 has a strong capacity for mutation, affecting both non-structural and structural proteins. Notably, the S protein, which is required for ACE2-dependent entry of SARS-CoV-2 into host cells, may be particularly prone to mutation, thereby favoring virus evolution and persistence[50]. Furthermore, SARS-CoV-2 may increase oxidative stress in COVID-19 patients either *via* inhibition of the conversion of angiotensin II to angiotensin-(1-7) with the resultant generation of superoxide or due to an increased ratio of neutrophils to lymphocytes which drives the production of superoxide and hydroxyl radicals[30]. Given the established role of superoxide and ROS as key mediators of disease progression, it is notable that the impact of SARS-CoV-2 infection is often greater in patients with co-morbidities, such as diabetes and preexisting cardiovascular disease, which is likely to be at least partly determined by increased oxidative stress. Therefore, inhibition of viral protein binding to host cells has clear potential to reduce oxidative stress and confer substantial health benefits during the early stages of SARS-CoV-2 infection[51].

Inflammation in COVID-19

COVID-19 causes serious respiratory and extra-pulmonary complications, which are observed in tissues with varying levels of ACE2 receptor expression, with damage to those with low ACE2 expression likely mediated by the host inflammatory response rather than direct viral entry[52]. Systemic inflammation associated with COVID-19 is typically characterized by increased circulating cytokines, often referred to as 'cytokine storm' or 'cytokine release syndrome', the severity of which is linked to deterioration of patient health[53]. Several immune cell types, including innate macrophages, dendritic cells, natural killer cells, and adaptive T and B lymphocytes, produce cytokines in response to virus-specific binding of pathogen-associated molecular patterns (PAMPs) to pattern recognition receptors. The consequent innate immune response against the invading virus activates multiple signaling pathways and downstream transcription factors leading to the induction of genes encoding pro-inflammatory cytokines[54]. In this regard, SARS-CoV-2 infection is linked with a specific inflammatory response profile, characterized by a delayed release of chemokines and cytokines from macrophages, airway epithelial cells, and dendritic cells during the early phase, followed by later phase secretion of high levels of pro-inflammatory cytokines (e.g. interleukins, tumor necrosis factor) and chemokines (e.g., CCL2, CCL3, CCL5) in parallel with low levels of antiviral factors (e.g., interferons)[55]. Indeed, it seems likely that activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway is central to pro-inflammatory signaling driven by SARS-CoV-2 infection and may underlie increased susceptibility to COVID-19 progression[56]. Specifically, NF-κB is the priming signal for nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome activation[38],

a critical component of host viral immune defense against a variety of viruses, and dysregulation of which is linked to the pathogenesis of inflammatory disorders, including auto-inflammatory diseases, ARDS, and acute lung injury, which are characterized by major pyroptosis[57]. Indeed, NF-κB activation boosts the generation of pro-inflammatory cytokines and ROS, both of which promote cellular damage and are characteristic features of SARS-CoV-2 infection[58], whilst dysregulation of NF-κB signaling is reported to worsen and intensify COVID-19[59]. Furthermore, pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor (TNF), which play established roles in ARDS pathogenesis, are also linked with severe cytokine storm in COVID-19[60], which may promote NF-κB-dependent epithelial and endothelial cell apoptosis, together with vascular leakage, leading to the development of life-threatening complications including ARDS[61], acute cardiac injury (e.g., myocarditis, myocardial infarction, cardiac arrest), sepsis, multi-organ failure, ischemic stroke, and acute pulmonary embolism, in addition to secondary infections such as bacterial pneumonia[62]. In this regard, it is notable that a significant proportion of COVID-19-related morbidity and mortality is linked with cardiovascular dysfunction, most likely occurring secondary to systemic inflammation. Indeed, multisystem inflammatory syndrome in children (MIS-C), which is observed in some individuals following SARS-CoV-2 infection and is clinically similar to Kawasaki Disease, provides direct evidence of the potential impact of inflammation related to COVID-19 on the cardiovascular system, with this condition characterized by cardiogenic shock and medium-sized artery vasculitis[63,64]. Indeed, circulating levels of C-reactive protein, an established inflammatory marker linked with cardiovascular disease, may independently predict severe or critical COVID-19, whilst D-dimer levels, indicative of thrombosis, may accurately predict in-hospital death due to COVID-19[65]. Furthermore, there is mounting evidence of increased risk of cardiovascular events post-acute COVID-19, which is not limited to patients hospitalized during the acute phase[66,67].

GLP-1 Receptor Agonists

GLP-1 is a 30-31 amino acid incretin peptide hormone produced primarily by three tissues in the human body: enteroendocrine L-cells in the distal intestine, pancreatic alpha cells, and the central nervous system[34]. Enteroendocrine L-cells generate GLP-1 in two forms, GLP-1 (7-36) amide and GLP-1 (7-37), both of which are physiologically active, although the former is predominant. During fasting, circulating GLP-1 concentrations are low (5-10 pmol/L), but are significantly increased (15-50 pmol/L) by feeding in a glucose-dependent manner. The half-life of native GLP-1 in the circulation is only ~ 2 minutes due to the rapid cleavage of alanine at the second residue by dipeptidyl peptidase-4 (DPP-4), resulting in the generation of inactive GLP-1 (9-36) amide or GLP-1 (9-37). Indeed, only 10-15% of secreted GLP-1 reaches the systemic circulation[68], resulting in a short period of biological activity. Once released, GLP-1 binds to and activates the GLP-1R, a seven-transmembrane G protein-coupled receptor, which is expressed in a variety of tissues, including pancreatic islets, heart, vasculature, liver, and central nervous system[69], and in inflammatory cells with preferential macrophage expression[70]. Further to their established insulinotropic benefits in reducing hyperglycemia and insulin resistance, GLP-1R agonists are increasingly employed in clinical practice to treat patients with T2DM[71,72]. Six GLP-1R agonists are currently approved for clinical use: exenatide twice daily, lixisenatide once daily, liraglutide once daily, exenatide once weekly, dulaglutide once weekly, and semaglutide once weekly[73]. They are highly effective in controlling blood glucose levels in a glucose-dependent manner, thereby minimizing the risk of hypoglycemia, and are associated with limited side effects, of which gastrointestinal symptoms are most common but typically transient in nature[74].

In addition to its metabolic actions, GLP-1 is widely reported to exert pleiotropic effects, particularly on the cardiovascular and central nervous systems, in both health and disease. For example, stress-induced increases in heart rate and blood pressure are linked to GLP-1 action in the brain, including stimulation of GLP-1-producing neurons[75], whilst GLP-1Rs confers cardioprotection against remodeling stresses, such as ischemia and diabetes[76,77]. GLP-1R activation also has established neuroprotective properties with potential clinical applications, including prevention or treatment of neurodegenerative illnesses, such as Alzheimer's and Parkinson's disease, as well as post-stroke rehabilitation[78]. In this regard, it is important to note that individuals with COVID-19 and preexisting diabetes demonstrate a two-fold greater risk of mortality[79], highlighting the significant influence of comorbidities on COVID-19

disease progression and severity. Given that prognosis after SARS-CoV-2 infection may be determined by effective clinical management of cytokine storm and that GLP-1R agonists are known to preferentially reduce cytokine production and inflammation, which is associated with improved lung function[80], it seems logical to suggest that these agents could be effective in improving outcomes in COVID-19 patients.

Anti-Inflammatory and Antioxidant Effects of GLP-1R Agonists

Amongst the number of pleiotropic actions exerted by GLP-1R agonists, anti-inflammatory effects are significant and largely mediated by inhibition of NF-κB-dependent cytokine release[38,81], a key driver of cytokine storm linked with SARS-CoV-2 infection. For example, in a rat model of experimental diabetes, renal NF-κB expression was inhibited by the GLP-1 analogue, exendin-4, and associated with attenuation of nephropathy[82], whilst liraglutide reversed NF-κB-mediated vascular inflammation in angiotensin II infused hypertensive mice *via* reduced expression of endothelial adhesion molecules, including vascular cell adhesion protein 1[84]. Notably, the anti-inflammatory benefits of exendin-4 are evident in both normoglycemia and hyperglycemia, as indicated by attenuation of adverse extracellular matrix remodeling and diastolic dysfunction in both experimental models of both myocardial infarction and diabetes, occurring independently of parallel metabolic changes and mediated *via* specific reduction of cardiac macrophage infiltration[21,22]. Similarly, liraglutide and exendin-4 are reported to mitigate atherosclerosis development in mice by inhibition of vascular monocyte adhesion and macrophage infiltration[77,84], whilst liraglutide-mediated reduction of lipopolysaccharide-induced sepsis is not evident in GLP-1R $^{-/-}$ mice[85], indicating that the apparent anti-inflammatory effects of GLP-1R agonists are mediated by GLP-1R stimulation. Importantly, these actions, which are widely evident in experimental models, are also observed in the clinical setting. For example, GLP-1R agonists are reported to reduce circulating concentrations of pro-inflammatory cytokines, such as IL-1β and TNF-α, in obese type 2 diabetic patients *vs.* patients receiving standard glycemic control therapy[72]. Similarly, both liraglutide and exendin-4 reduce the expression of pro-inflammatory cytokines, IL-1β, IL-6, TNF-α and MCP-1 in human mononuclear cells, in parallel with increased expression of adiponectin, which promotes established anti-inflammatory actions[86,87]. In this regard, exendin-4 attenuates macrophage-mediated adipose tissue inflammation *via* specific inhibition of NF-κB-dependent cytokine secretion[88], suggesting that GLP-1R agonists modulate both immune cell and adipose tissue function independently of their well-established actions on glycemic control. Indeed, GLP-1R activation in T2DM may specifically inhibit NLRP3 inflammasome-dependent inflammation in perivascular adipose tissue, characterized by NF-κB-mediated upregulation of cleaved caspase-1, IL-1, and IL-18[89]. Consistent with this observation, T2DM patients treated with GLP-1R agonists display increased plasma levels of anti-inflammatory adipokines, such as adiponectin, together with reduced pro-inflammatory cytokines[86].

In addition to their evident anti-inflammatory effects, emerging evidence indicates that GLP-1R agonists may also confer important antioxidant effects with significance to SARS-CoV-2 infection. For example, liraglutide is reported to promote antioxidant and anti-inflammatory properties in angiotensin II-treated mice, which is linked with the attenuation of hypertension-induced cardiac hypertrophy and vascular fibrosis[83]. Furthermore, treatment of human umbilical vein endothelial cells with native GLP-1 (7-36) reduced high glucose-induced oxidative stress *via* inhibition in NADPH oxidase activation[90], whilst liraglutide promotes antioxidant effects on platelets, characterized by decreased ROS and increased nitric oxide generation, and associated with inhibition of platelet aggregation[91]. Consistent with its reported anti-inflammatory actions, exendin-4 reduces ROS formation in human monocytes, assessed by malondialdehyde levels[87], *via* inhibition of NADPH oxidase activity and stimulation of antioxidant enzymes, glutathione peroxidase and superoxide dismutase[92]. Taken together, these findings support the emerging consensus that GLP-1R agonists hold significant therapeutic potential beyond their current application for glycemic control, by specifically targeting pro-inflammatory and pro-oxidative aspects, particularly in relation to diabetic vascular complications and cardiovascular disease.

GLP-1 Receptor Agonists as Promising Drugs Against COVID-19

Given that preexisting T2DM is a significant determinant of poor prognosis in COVID-19 patients[58], and GLP-1R agonists, which are now widely prescribed for glycemic control, have established

anti-inflammatory and antioxidant actions, it is possible to suggest that they may also confer therapeutic benefit against SARS-CoV-2 infection and COVID-19 (Figure 2). As the GLP-1R is ubiquitously expressed, including in lungs, and the activation inhibits cytokine release, it has been proposed that increased systemic GLP-1 concentrations may be beneficial against the development and progression of acute obstructive pulmonary disease associated with severe COVID-19[93]. Although GLP-1R agonists are unlikely to directly impact respiratory SARS-CoV-2 infection, their potent anti-inflammatory properties hold clear potential to dampen the consequent excessive systemic inflammatory response[38]. It is particularly notable that GLP-1R activation appears to be highly significant in monocyte and macrophages, which represent the most abundant immune cell types in the lungs of COVID-19 patients. In this regard, GLP-1R agonists have been shown to inhibit cytokine production and reduce pulmonary inflammation, which may be particularly advantageous in COVID-19 patients with preexisting atherosclerosis, obesity, or T2DM, which are associated with aberrant inflammation and poor prognosis. Indeed, anti-inflammatory actions of liraglutide are associated with preserved respiratory function in rodents subjected to LPS-induced acute lung injury *via* inhibition of the NLRP3 pathway[94], whilst improved lung function and mortality are evident in mice subjected to chronic obstructive pulmonary disease and liraglutide treatment[95]. Consistent with these experimental findings, native GLP-1 (7-36) is reported to stimulate protein kinase A-induced surfactant secretion by human type 2 pneumocytes, whose primary role is protection against inflammatory-mediated cellular damage, such as that observed after SARS-COV-2 infection[96]. Similarly, pulmonary vascular remodeling, a key feature of severe COVID-19, is reduced by liraglutide treatment in experimental monocrotaline-induced pulmonary arterial hypertension *via* activation of endothelial nitric oxide synthase[97]. It is interesting to note that SARS-CoV-2 infection typically promotes a

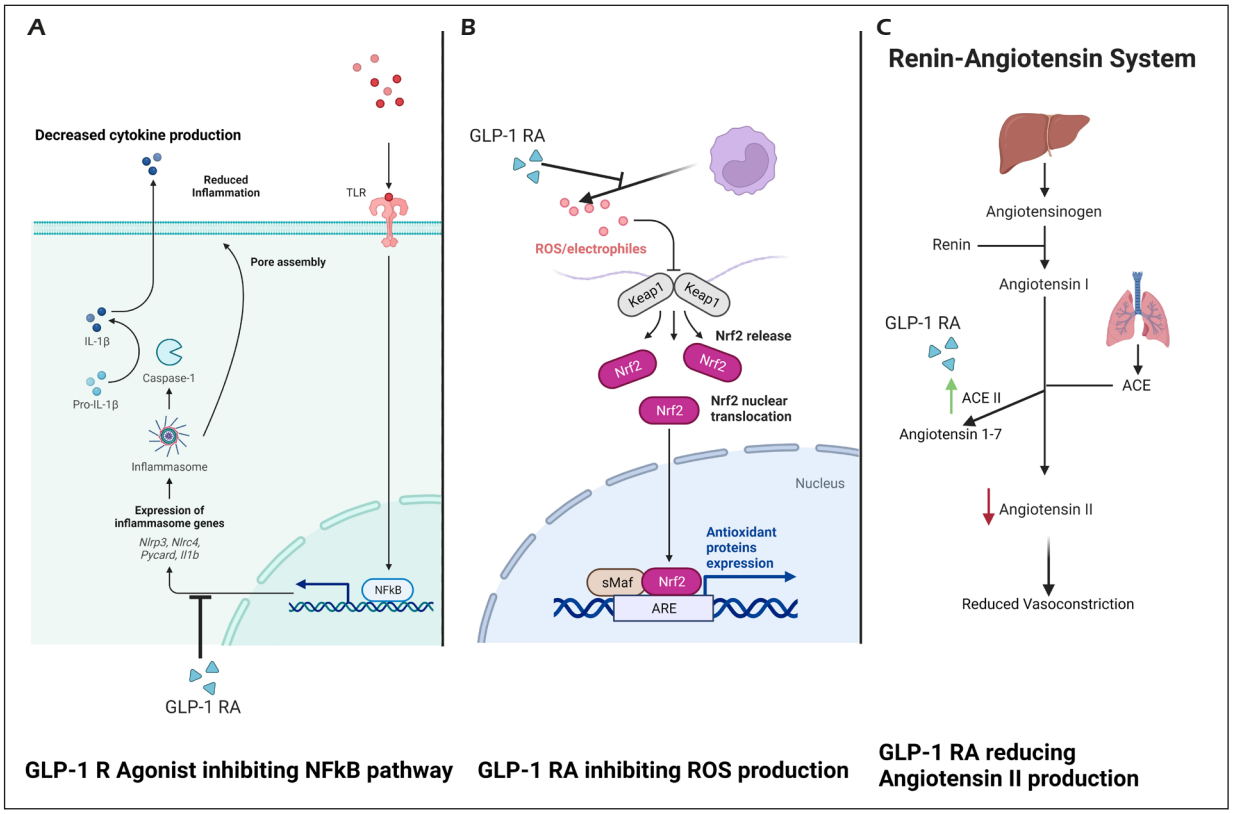

Figure 2. Proposed mechanisms by which GLP-1R agonists may protect against inflammation and oxidative stress associated with COVID-19. Emerging evidence indicates that GLP-1R agonists (GLP-1 RA) may reduce (**A**) NF-κB-mediated proinflammatory signalng, (**B**) oxidative stress *via* inhibition of ROS generation and/or promotion of endogenous antioxidants, and (**C**) renin-angiotensin-aldosterone activation *via* ACE2 upregulation, which all appear to be central to SARS-CoV-2 pathogenesis and consequent thrombotic and inflammatory complications.

switch in cell metabolism towards a predominantly glycolytic phenotype, which promotes virus proliferation and is driven largely by mitochondrial ROS generation and subsequent stabilization of hypoxia-inducible factor-1α. It, therefore, seems possible that GLP-1R agonists, which impact both metabolic and oxidative signaling, may also reduce direct consequences of SARS-CoV-2 cell entry. Indeed, such metabolic changes in monocytes and macrophages, which are preferential targets for GLP-1R activation, further to SARS-CoV-2 infection, may also impair T cell responsiveness and diminish airway epithelial cell survival[98]. Taken together, these initial data are intriguing and clearly supportive of the potential repurposing of GLP-1R agonists for the management of respiratory complications linked with SARS-CoV-2 infection[80].

In addition to the direct anti-inflammatory effects of GLP-1R agonists on pulmonary inflammation and function, it appears that these drugs may also reduce respiratory infection *via* modulation of ACE2, a cell-bound protease with abundant expression in alveolar epithelium, enterocytes, and blood vessels, which catalyzes the conversion of angiotensin II to angiotensin (1-7). Indeed, liraglutide is reported to upregulate the expression of ACE2 in the lungs of diabetic rats[99], thereby counteracting pro-inflammatory and pro-fibrotic actions of renin-angiotensin-aldosterone system activation[100]. In this regard, it has been suggested that GLP-1R mediated induction of ACE2 could limit lung injury in COVID-19 by opposing SARS-CoV-2 infection-related reduction in ACE2 expression levels and reducing consequent immune cell over-activation and ARDS[101]. However, it is crucial to note that as the ACE2 receptor represents the primary mechanism by which SARS-CoV-2 enters and replicates within airway epithelium[10], there is a risk that induction of ACE2 expression by GLP-1R agonists could exacerbate COVID-19. As such, further experimental and clinical studies are needed to elucidate the precise relationship between ACE2 and ACE2 receptor expression in relation to SARS-CoV-2 infection and GLP-1R activation.

In addition to the likely direct anti-inflammatory and antioxidant actions of GLP-1R agonists in the context of SARS-CoV-2 infection, it is important to consider that obesity and T2DM, for which these drugs are recommended treatments, predispose to increased severity of COVID-19[102] Therefore, the established metabolic benefits of GLP-1R agonists in promoting weight loss *via* normalization of insulin and glucagon signaling, which are associated with reduction of systemic inflammation and improved immune function[103], are likely to enhance COVID-19 prognosis. In this regard, early reports of the clinical effects of GLP-1R agonists in this setting are encouraging. One large-scale study[39] of 12,446 SARS-COV-2 positive T2DM patients, indicated that pre-existing prescription of either a GLP-1R agonist or sodium/glucose cotransporter-2 (SGLT2) inhibitor lowered both 60-day mortality and hospitalization in comparison to patients receiving DPP4 inhibitor therapy. Similarly, a meta-analysis of T2DM patients admitted to hospitals with COVID-19 indicated reduced mortality in those using GLP-1R agonists *vs.* standard glycemic control therapy, with particular benefits observed in patients with additional cardiovascular risk factors[104]. Indeed, atherosclerosis, which is largely viewed as an inflammatory disease, may be considered a comorbidity contributing to an increased risk of COVID-19 infection and poor outcomes. In this regard, atherogenic inflammatory profiles, characterized by aberrant cytokine release and immune cell activation, are reported to determine COVID-19 severity[105], which may be impacted by established anti-inflammatory actions of GLP-1R agonists to reduce atherosclerotic disease[106]. Although current data supporting the potential application of GLP-1R agonists for treatment of COVID-19 is limited to T2DM cohorts, this is likely to extend to non-diabetic patients given that their anti-inflammatory and antioxidant actions are also evident in normoglycemia. Nonetheless, further research is required to assess whether this class of drugs may represent a safe and effective therapeutic option for the management of both diabetic and non-diabetic patients exposed to SARS-CoV-2 infection.

Conclusions

COVID-19 continues to represent a significant public health concern that is evident worldwide and associated with severe complications driven by aberrant inflammatory responses and multi-organ dysfunction, which are particularly prominent in T2DM and obese individuals. Although some drugs have been shown to confer benefits against COVID-19, more specific and effective treatments, especially against chronic aspects, are urgently needed. In this regard, GLP-1R agonists, which are primarily used for the management of glycemia in T2DM, confer anti-inflammatory and antioxidant effects on multiple organ systems, including cardiovascular, respiratory, renal, and endocrine,

in addition to their established metabolic actions. These properties, which are apparent in both normoglycemic and hyperglycemic conditions, together with emerging clinical evidence, highlight GLP-1R agonists as a potential therapeutic option for SARS-CoV-2 and COVID-19, particularly in patients with comorbidities. Detailed mechanisms by which GLP-1R activation may interact with SARS-CoV-2 infection and impact the development and progression of COVID-19 remain still unclear. Nonetheless, it is important to recognize the significant additional potential benefits of GLP-1R agonists, beyond glucose control in T2DM, towards effective treatment of comorbidities and other inflammatory disorders, which appear to include both acute and chronic COVID-19.

Ethical Approval
Not applicable.

Informed Consent
Not applicable.

Conflict of Interest
No competing interests were disclosed.

Authors' Contributions
Rawan Abudalo, Abdelrahim Alqudah, and Rabaa Athamneh performed the review article design and executed article drafting and writing. Cathal Roarty revised the draft and drew figures. The final revision was executed by David Grieve. The final version of the article was approved by all authors for publication.

Funding
The authors declared that no grants were involved in supporting this work.

Availability of Data and Materials
Not applicable.

References

1) Durankuş F, Aksu E. Effects of the COVID-19 pandemic on anxiety and depressive symptoms in pregnant women: a preliminary study. J Matern Fetal Neonatal Med 2022; 35: 205-211.
2) Gümüş H, Erat T, Öztürk İ, Demir A, Koyuncu I. Oxidative stress and decreased Nrf2 level in pediatric patients with COVID-19. J Med Virol 2022; 94: 2259-2264.
3) Ukwenya VO, Adelakun SA, Fuwape TA, Adeagbo AS. The impact of deranged glucose metabolism and diabetes in the pathogenesis and prognosis of the novel SARS-CoV-2: A systematic review of literature. Curr Diabetes Rev 2022; 18: 101-112.
4) Alnefaie A, Albogami S. Current approaches used in treating COVID-19 from a molecular mechanisms and immune response perspective. Saudi Pharm J 2020; 28: 1333-1352.
5) Ranard LS, Fried JA, Abdalla M, Anstey DE, Givens RC, Kumaraiah D, Kodali SK, Takeda K, Karmpaliotis, D, Rabbani LE, Sayer G, Kirtane AJ, Leon MB, Schwartz A, Uriel N, Masoumi A. Approach to acute cardiovascular complications in COVID-19 infection. Circ Heart Fail 2020; 13: e007220.
6) Akhmerov A, Marbán E. COVID-19 and the heart. Circ Res 2020; 126: 1443-1455.
7) Guo YR, Cao, QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan, KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020; 7: 1-10.
8) Morens DM, Breman JG, Calisher CH, Doherty PC, Hahn BH, Keusch GT, Kramer LD, LeDuc JW, Monath TP, & Taubenberger JK. The origin of COVID-19 and why it matters. Am J Trop Med Hyg 2020; 103: 955-959.
9) Kulanthaivel S, Kaliberdenko VB, Balasundaram K, Shterenshis MV, Scarpellini E, Abenavoli L. Tocilizumab in SARS-CoV-2 patients with the syndrome of cytokine storm: A narrative review. Rev Recent Clin Trials 2021; 16: 138-145.
10) Sawa T, Akaike T. What triggers inflammation in COVID-19? Elife 2022; 11: e76231.
11) Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.
12) Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426: 450-454.
13) Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog 2018; 14: e1007236.
14) Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271-280.
15) Heurich A, Hofmann-Winkler H, Gierer S, Liepold T, Jahn O, Pöhlmann S. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. J Virol 2014; 88: 1293-1307.
16) Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, Campagnole-Santos MJ. The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1-7). Physiol Rev 2018; 98: 505-553.

17) Horiuchi M, Akishita M, Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. Hypertension 1999; 33: 613-621.
18) Glowacka I, Bertram S, Herzog P, Pfefferle S, Steffen I, Muench MO, Simmons G, Hofmann H, Kuri T, Weber F. Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. J Virol 2010; 84: 1198-1205.
19) Papp M, Li X, Zhuang J, Wang R, Uhal BD. Angiotensin receptor subtype AT1 mediates alveolar epithelial cell apoptosis in response to ANG II. Am J Physiol Lung Cell Mol Physiol 2002; 282: L713-L718.
20) Welch WJ. Angiotensin II–Dependent Superoxide: Effects on Hypertension and Vascular Dysfunction. Hypertension 2008; 52: 51-56.
21) Marchesi C, Paradis P, Schiffrin EL. Role of the renin–angiotensin system in vascular inflammation. Trends Pharmacol Sci 2008; 29: 367-374.
22) Wang Y, Wang Y, Luo W, Huang L, Xiao J, Li F, Qin S, Song X, Wu Y, Zeng Q. A comprehensive investigation of the mRNA and protein level of ACE2, the putative receptor of SARS-CoV-2, in human tissues and blood cells. Int J Med Sci 2020; 17: 1522-1531.
23) Pesaresi M, Pirani F, Tagliabracci A, Valsecchi M, Procopio A, Busardò F, Graciotti L. SARS-CoV-2 identification in lungs, heart and kidney specimens by transmission and scanning electron microscopy. Eur Rev Med Pharmacol Sci 2020; 24: 5186-5188.
24) Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-481.
25) Wong RSY. Inflammation in COVID-19: from pathogenesis to treatment. Int J Clin Exp Pathol 2021; 14: 831-844.
26) Quirch M, Lee J, Rehman S. Hazards of the cytokine storm and cytokine-targeted therapy in patients with COVID-19: Review. J Med Internet Res 2020; 22: e20193.
27) Tan LY, Komarasamy TV, Rmt Balasubramaniam V. Hyperinflammatory immune response and COVID-19: A double edged sword. Front Immunol 2021; 12: 742941.
28) Chernyak BV, Popova EN, Prikhodko AS, Grebenchikov OA, Zinovkina LA, Zinovkin RA. COVID-19 and oxidative stress. Biochem (Mosc) 2020; 85: 1543-1553.
29) Wieczfinska J, Kleniewska P, Pawliczak R. Oxidative stress-related mechanisms in SARS-CoV-2 infections. Oxid Med Cell Longev 2022; 2022: 5589089.
30) Alam MS, Czajkowsky DM. SARS-CoV-2 infection and oxidative stress: Pathophysiological insight into thrombosis and therapeutic opportunities. Cytokine Growth Factor Rev 2022; 63: 44-57.
31) Cecchini R, Cecchini AL. SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. Med Hypotheses 2020; 143: 110102.
32) Mohiuddin M, Kasahara K. The emerging role of oxidative stress in complications of COVID-19 and potential therapeutic approach to diminish oxidative stress. Respir Med 2021; 187: 106605.
33) Dhir G, Cusi K. Glucagon like peptide-1 receptor agonists for the management of obesity and non-alcoholic fatty liver disease: a novel therapeutic option. J Investig Med 2018; 66: 7-10.
34) Zhao X, Wang M, Wen Z, Lu Z, Cui L, Fu C, Xue H, Liu Y, Zhang Y. GLP-1 receptor agonists: Beyond their pancreatic effects. Front Endocrinol (Lausanne) 2021; 12: 721135.
35) Tate M, Robinson E, Green BD, McDermott BJ, Grieve DJ. Exendin-4 attenuates adverse cardiac remodelling in streptozocin-induced diabetes via specific actions on infiltrating macrophages. Basic Res Cardiol 2016; 111: 1-13.
36) Robinson E, Cassidy RS, Tate M, Zhao Y, Lockhart S, Calderwood D, Church R, McGahon MK, Brazil DP, McDermott BJ, Green BD, Grieve DJ. Exendin-4 protects against post-myocardial infarction remodelling via specific actions on inflammation and the extracellular matrix. Basic Res Cardiol 2015; 110: 1-15.
37) Que Q, Guo X, Zhan L, Chen S, Zhang Z, Ni X, Ye B, Wan S. The GLP-1 agonist, liraglutide, ameliorates inflammation through the activation of the PKA/CREB pathway in a rat model of knee osteoarthritis. J Inflamm (Lond) 2019; 16: 13.
38) Banerjee Y, Pantea Stoian A, Silva-Nunes J, Sonmez, A., Rizvi A., Janez, A., Rizzo M. The role of GLP-1 receptor agonists during COVID-19 pandemia: a hypothetical molecular mechanism. Expert Opin Drug Saf 2021; 20: 1309-1315.
39) Kahkoska AR, Abrahamsen TJ, Alexander GC, Tellen DB, Christopher GC, Melissa AH, Klara RK, Hemalkumar M, Joshua DM, Richard AM, Til S, Kvist KB, John BB. Association between glucagon-like peptide 1 receptor agonist and sodium-glucose cotransporter 2 inhibitor use and COVID-19 outcomes. Diabetes Care 2021; 44: 1564-1572.
40) Wang K, Gao Y, Wang C, Liang M, Liao Y, Hu K. Role of oxidative stress in varicocele. Front Genet 2022; 13: 850114.
41) Shields HJ, Traa A, Van Raamsdonk JM. Beneficial and detrimental effects of reactive oxygen species on lifespan: A comprehensive review of comparative and experimental studies. Front Cell Dev Biol 2021; 9: 628157.
42) Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative stress: Harms and benefits for human health. Oxid Med Cell Longev 2017; 2017: 1-13.
43) Ebrahimi S, Alalikhan A, Aghaee-Bakhtiari SH, Hashemy SI. The redox modulatory effects of SP/NK1R system: Implications for oxidative stress-associated disorders. Life Sci 2022; 296: 120448.
44) Percário S, da Silva Barbosa A, Varela EL, Gomes, AR, Ferreira, ME, de Nazaré Araújo Moreira T, Dolabela, M. Oxidative stress in Parkinson's disease: Potential benefits of antioxidant supplementation. Oxid Med Cell Longev 2020; 2020: 1-23.

45) Cioffi F, Adam RHI, Broersen K. Molecular mechanisms and genetics of oxidative stress in Alzheimer's disease. J Alzheimers Dis 2019; 72: 981-1017.
46) Zhang M, Shah AM. ROS signaling between endothelial cells and cardiac cells. Cardiovasc Res 2014; 102: 249-257.
47) Chang R, Mamun A, Dominic A, Le NT. SARS-CoV-2 mediated endothelial dysfunction: The potential role of chronic oxidative stress. Front Physiol 2020; 11: 605908
48) Saheb Sharif-Askari N, Saheb Sharif-Askari F, Mdkhana B, Hussain Alsayed HA, Alsafar H, Alrais ZF,Hamid Q, Halwani R. Upregulation of oxidative stress gene markers during SARS-COV-2 viral infection. Free Radic Biol Med 2021; 172: 688-698.
49) Fernandes IG, de Brito CA, Dos Reis VMS, Sato MN, Pereira NZ. SARS-CoV-2 and other respiratory viruses: What does oxidative stress have to do with it? Oxid Med Cell Longev 2020; 2020: 1-13.
50) Bakadia BM, Boni BOO, Ahmed AAQ, Yang G. The impact of oxidative stress damage induced by the environmental stressors on COVID-19. Life Sci 2021; 264: 118653.
51) Suhail S, Zajac J, Fossum C, Lowater H, McCracken C, Severson N, Laatsch B, Narkiewicz-Jodko A, Johnson B, Liebau J, Bhattacharyya S, Hati S. Role of oxidative stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) infection: A review. Protein J 2020; 39: 644-656.
52) Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical characteristics of multisystem inflammatory syndrome in adults: A systematic review: A systematic review. JAMA Netw Open 2021; 4: e2126456.
53) Kunnumakkara AB, Rana V, Parama D, Banik K, Girisa S, Henamayee S, Thakur K, Dutta U, Garodia P, Gupta SC, Aggarwa BB. COVID-19, cytokines, inflammation, and spices: How are they related? Life Sci 2021; 284: 119201.
54) Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; What we know so far. Front Immunol 2020; 11: 1446.
55) Castelli V, Cimini A, Ferri C. Cytokine storm in COVID-19: "when you come out of the storm, you won't be the same person who walked in." Front Immunol 2020; 11: 2132.
56) Su CM, Wang L, Yoo D. Activation of NF-κB and induction of proinflammatory cytokine expressions mediated by ORF7a protein of SARS-CoV-2. Sci Rep 2021; 11: 13464.
57) Zhao N, Di B, Xu LL. The NLRP3 inflammasome and COVID-19: Activation, pathogenesis and therapeutic strategies. Cytokine Growth Factor Rev 2021; 61: 2-15.
58) Sazgarnejad S, Yazdanpanah N, Rezaei N. Anti-inflammatory effects of GLP-1 in patients with COVID-19. Expert Rev Anti Infect Ther 2022; 20: 373-381.
59) Amin S, Aktar S, Rahman MM, Chowdhury MMH. NLRP3 inflammasome activation in COVID-19: an interlink between risk factors and disease severity. Microbes Infect 2022; 24: 104913.
60) Shah A. Novel Coronavirus-induced NLRP3 inflammasome activation: A potential drug target in the treatment of COVID-19. Front Immunol 2020; 11: 1021.
61) Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: The current evidence and treatment strategies. Front Immunol 2020; 11: 1708.
62) Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, Rajagopal S, Pai AR, Kutty S. Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM consortium position paper. Front Immunol 2020; 11: 1648.
63) Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; 395: 1607-1608.
64) Diorio C, McNerney KO, Lambert M, Paessler M, Anderson EM, Henrickson SE, Chase J, Liebling EJ, Burudpakdee C, Lee JH, Balamuth FB, Blatz AM, Chiotos K, Fitzgerald JC, Giglia TM, Gollomp K, Odom John AR, Jasen C, Leng T, Petrosa W, Vella LA, Witmer C, Sullivan KE, Laskin BL, Hensley SE, Bassiri H, Behrens EM, Teachey DT. Evidence of thrombotic microangiopathy in children with SARS-CoV-2 across the spectrum of clinical presentations. Blood Adv 2020; 4: 6051-6063.
65) Kitakata H, Kohsaka S, Kuroda S, Nomura A, Kitai T, Yonetsu T, Torii S, Matsue Y, Matsumoto S. Inflammatory and hypercoagulable biomarkers and clinical outcomes in COVID-19 patients. J Clin Med 2021; 10: 3086.
66) Wang W, Wang CY, Wang SI, Wei JCC. Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks. EClinicalMedicine 2022; 53: 101619.
67) Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med 2022; 28: 583-590.
68) Sharma D, Verma S, Vaidya S, Kalia K, Tiwari V. Recent updates on GLP-1 agonists: Current advancements & challenges. Biomed Pharmacother 2018; 108: 952-962.
69) Fu Z, Gong L, Liu J, Wu J, Barrett EJ, Aylor KW, Liu Z. Brain endothelial cells regulate glucagon-like peptide 1 entry into the brain via a receptor-mediated process. Front Physiol 2020; 11: 555.
70) Chen J, Mei A, Liu X, Braunstein Z, Wei Y, Wang B, Duan L, Rao X, Rajagopalan S, Dong L, Zhong J. Glucagon-like peptide-1 receptor regulates macrophage migration in monosodium urate-induced peritoneal inflammation. Front Immunol 2022; 13: 772446.
71) He L, Wang J, Ping F, Yang N, Huang J, Li Y, Xu L, Li W, Zhang H. Association of glucagon-like peptide-1 receptor agonist use with risk of gallbladder and biliary diseases: A systematic review and meta-analysis of randomized clinical trials: A systematic review and meta-analysis of randomized clinical trials. JAMA Intern Med 2022; 182: 513-519.

72) Ishigaki Y, Strizek A, Aranishi T, Arai N, Imaoka T, Cai Z, Maegawa, H. Glucagon-like peptide-1 receptor agonist utilization in type 2 diabetes in japan: A retrospective database analysis (JDDM 57). Diabetes Ther 2021; 12: 345-361.
73) Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. Ther Adv Endocrinol Metab 2021; 12: 1-15.
74) Brunton SA, Wysham CH. GLP-1 receptor agonists in the treatment of type 2 diabetes: role and clinical experience to date. Postgrad Med 2020; 132: 3-14.
75) Holt MK, Rinaman L. The role of nucleus of the solitary tract glucagon-like peptide-1 and prolactin-releasing peptide neurons in stress: anatomy, physiology and cellular interactions. Br J Pharmacol 2022; 179: 642-658.
76) Eid RA, Alharbi SA, El-kott AF, Eleawa SM, Zaki MSA, El-Sayed F, Eldeen MA, Aldera H, Al-Shudiefat AR. Exendin-4 ameliorates cardiac remodeling in experimentally induced myocardial infarction in rats by inhibiting PARP1/NF-κB axis in A SIRT1-dependent mechanism. Cardiovasc Toxicol 2020; 20: 401-418.
77) Noyan-Ashraf MH, Shikatani EA, Schuiki I, Mukovozov I, Wu J, Li RK, Volchuk A, Robinson LA, Billia F, Drucker DJ, Husain M. A glucagon-like peptide-1 analog reverses the molecular pathology and cardiac dysfunction of a mouse model of obesity. Circulation 2013; 127: 74-85.
78) Augestad IL, Dekens D, Karampatsi D, Elabi O, Zabala A, Pintana H, Larsson M, Nyström T, Paul G, Darsalia V, Patrone C. Normalization of glucose metabolism by exendin-4 in the chronic phase after stroke promotes functional recovery in male diabetic mice. Br J Pharmacol 2022; 179: 677-694.
79) Israelsen SB, Pottegård A, Sandholdt H, Madsbad S, Thomsen RW, Benfield T. Comparable COVID-19 outcomes with current use of GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors among patients with diabetes who tested positive for SARS-CoV-2. Diabetes Obes Metab 2021; 23: 1397-1401.
80) Lee JH. Potential therapeutic effect of glucagon-like peptide-1 receptor agonists on COVID-19-induced pulmonary arterial hypertension. Med Hypotheses 2022; 158: 110739.
81) Ma J, Shi M, Zhang X, Liu X, Chen J, Zhang R, Wang X, Zhang H. GLP 1R agonists ameliorate peripheral nerve dysfunction and inflammation via p38 MAPK/NF κB signaling pathways in streptozotocin induced diabetic rats. Int J Mol Med 2018; 41: 2977-2985.
82) Kodera R, Shikata K, Kataoka HU, Takatsuka T, Miyamoto S, Sasaki M, Kajitani N, Nishishita S, Sarai K, Hirota D, Sato C, Ogawa D, Makino H. Glucagon-like peptide-1 receptor agonist ameliorates renal injury through its anti-inflammatory action without lowering blood glucose level in a rat model of type 1 diabetes. Diabetologia 2011; 54: 965-978.
83) Helmstädter J, Frenis K, Filippou K, Grill A, Dib M, Kalinovic S, Pawelke F, Kus K, Kröller-Schön S, Oelze M, Chlopicki S, Schuppan D, Wenzel P, Ruf W, Drucker DJ, Münzel T, Daiber A, Steven S. Endothelial GLP-1 (glucagon-like peptide-1) receptor mediates cardiovascular protection by liraglutide in mice with experimental arterial hypertension. Arterioscler Thromb Vasc Biol 2020; 40: 145-158.
84) Arakawa M, Mita T, Azuma K, Ebato C, Goto H, Nomiyama T, Fujitani Y, Hirose T, Kawamori R, Watada H. Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. Diabetes 2010; 59: 1030-1037.
85) Steven S, Hausding M, Kröller-Schön S, Mader M, Mikhed Y, Stamm P, Zinßius E, Pfeffer A, Welschof P, Agdauletova S, Sudowe S, Li H, Oelze M, Schulz E, Klein T, Münzel T, Daiber A. Gliptin and GLP-1 analog treatment improves survival and vascular inflammation/dysfunction in animals with lipopolysaccharide-induced endotoxemia. Basic Res Cardiol 2015; 110: 6.
86) Hogan AE, Gaoatswe G, Lynch L, Corrigan MA, Woods C, O'Connell J, O'Shea D. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. Diabetologia 2014; 57: 781-784.
87) Chaudhuri A, Ghanim H, Vora M, Sia CL, Korzeniewski K, Dhindsa S, Makdissi A, Dandona P. Exenatide exerts a potent antiinflammatory effect. J Clin Endocrinol Metab 2012; 97: 198-207.
88) Guo C, Huang T, Chen A, Chen X, Wang L, Shen F, Gu X. Glucagon-like peptide 1 improves insulin resistance in vitro through anti-inflammation of macrophages. Braz J Med Biol Res 2016; 49: e5826.
89) Chen X, Huang Q, Feng J, Xiao Z, Zhang X, Zhao L. GLP-1 alleviates NLRP3 inflammasome-dependent inflammation in perivascular adipose tissue by inhibiting the NF-κB signalling pathway. J Int Med Res 2021; 49: 1-10.
90) Wang R, Lu L, Guo Y, Lin F, Chen H, Chen W, Chen M. Effect of glucagon-like peptide-1 on high-glucose-induced oxidative stress and cell apoptosis in human endothelial cells and its underlying mechanism. J Cardiovasc Pharmacol 2015; 66: 135-140.
91) Barale C, Buracco S, Cavalot F, Frascaroli C, Guerrasio A, Russo I. Glucagon-like peptide 1-related peptides increase nitric oxide effects to reduce platelet activation. Thromb Haemost 2017; 117: 1115-1128.
92) Bułdak L, Łabuzek K, Bułdak RJ, Machnik G, Bołdys A, Okopień B. Exenatide (a GLP-1 agonist) improves the antioxidative potential of in vitro cultured human monocytes/macrophages. Naunyn Schmiedebergs Arch Pharmacol 2015; 388: 905-919.
93) G. Elkabily A, M. Sebaiy M. A suggestion of using Ang-(1-7) and/or GLP-1 receptor agonists in high mortality patients with COVID-19. Tren Med 2020; 20: 1-3.
94) Zhou F, Zhang Y, Chen J, Hu X, Xu Y. Liraglutide attenuates lipopolysaccharide-induced acute lung injury in mice. Eur J Pharmacol 2016; 791: 735-740.

95) Viby NE, Isidor MS, Buggeskov KB, Poulsen SS, Hansen JB, Kissow H. Glucagon-like peptide-1 (GLP-1) reduces mortality and improves lung function in a model of experimental obstructive lung disease in female mice. Endocrinology 2013; 154: 4503-4511.
96) Vara E, Arias-Díaz J, Garcia C, Balibrea JL, Blázquez E. Glucagon-like peptide-1(7-36) amide stimulates surfactant secretion in human type II pneumocytes. Am J Respir Crit Care Med 2001; 163: 840-846.
97) Lee MY, Tsai KB, Hsu JH, Shin SJ, Wu JR, Yeh JL. Liraglutide prevents and reverses monocrotaline-induced pulmonary arterial hypertension by suppressing ET-1 and enhancing eNOS/sGC/PKG pathways. Sci Rep 2016; 6: 31788.
98) Codo AC, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, Prodonoff JS, Carregari VC, de Biagi Junior CA, Crunfli F, Jimenez Restrepo JL, Vendramini PH, Reis-de-Oliveira G, Bispo dos Santos K, Toledo-Teixeira DA, Parise PL, Martini MC, Marques RE, Carmo HR, Borin A, Coimbra LD, Boldrini VO, Brunetti NS, Vieira AS, Mansour E, Ulaf RG, Bernardes AF, Nunes TA, Ribeiro LC, Palma AC, Agrela MV, Moretti ML, Sposito AC, Pereira FB, Velloso LA, Vinolo MAR, Damasio A, Proença-Módena JL, Carvalho RF, Mori MA, Martins-de-Souza D, Nakaya HI, Farias AS, Moraes-Vieira PM. Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis-dependent axis. Cell Metab 2020; 32: 437-446.e5.
99) Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, Santisteban P, González-Matías LC, Vigo E, Mallo F. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. Endocrinology 2015; 156: 3559-3569.
100) Akhtar S, Benter IF, Danjuma MI, Doi SAR, Hasan SS, Habib AM. Pharmacotherapy in COVID-19 patients: a review of ACE2-raising drugs and their clinical safety. J Drug Target 2020; 28: 683-699.
101) Mirabelli M, Chiefari E, Puccio L, Foti DP, Brunetti A. Potential benefits and harms of novel antidiabetic drugs during COVID-19 crisis. Int J Environ Res Public Health 2020; 17: 3664.
102) Belančić A, Kresović A, Rački V. Potential pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity. Obes Med 2020; 19: 100259.
103) Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 2018; 27: 740-756.
104) Hariyanto TI, Intan D, Hananto JE, Putri C, Kurniawan A. Pre-admission glucagon-like peptide-1 receptor agonist (GLP-1RA) and mortality from coronavirus disease 2019 (Covid-19): A systematic review, meta-analysis, and meta-regression. Diabetes Res Clin Pract 2021; 179: 109031.
105) Vinciguerra M, Romiti S, Fattouch K, De Bellis A, Greco E. Atherosclerosis as pathogenetic substrate for SARS-Cov2 cytokine storm. J Clin Med 2020; 9: 2095.
106) Rakipovski G, Rolin B, Nøhr J, Klewe I, Frederiksen KS, Augustin R, Hecksher-Sørensen J, Ingvorsen C, Polex-Wolf J, Knudsen LB. The GLP-1 analogs liraglutide and semaglutide reduce atherosclerosis in ApoE-/- and LDLr-/- mice by a mechanism that includes inflammatory pathways. JACC Basic Transl Sci 2018; 3: 844-857.