Journal of *Xenobiotics*

MDPI

Review

Pathogenesis and Management of COVID-19

Khalid O. Alfarouk [1,2,*], Sari T. S. AlHoufie [3], Samrein B. M. Ahmed [4], Mona Shabana [5], Ahmed Ahmed [6], Saad S. Alqahtani [7], Ali S. Alqahtani [8], Ali M. Alqahtani [9], AbdelRahman M. Ramadan [10], Mohamed E. Ahmed [2,11], Heyam S. Ali [12], Adil Bashir [1,13], Jesus Devesa [14], Rosa A. Cardone [15], Muntaser E. Ibrahim [13], Laurent Schwartz [16] and Stephan J. Reshkin [15]

1 Hala Alfarouk Cancer Center, Department of Evolutionary Pharmacology and Tumor Metabolism, Khartoum 11123, Sudan; derma55@yahoo.com
2 Research Center, Zamzam University College, Khartoum 11123, Sudan; rector@zamzam.edu.sd
3 Medical Laboratories Technology Department, College of Applied Medical Sciences, Taibah University, Medina 42353, Saudi Arabia; shoufie@taibahu.edu.sa
4 College of Medicine, University of Sharjah, Sharjah 27272, United Arab Emirates; samahmed@sharjah.ac.ae
5 Pharmacology Department, Faculty of Medicine, Fayoum University, Fayoum 63514, Egypt; mfs01@fayoum.edu.eg
6 Department of Oesphogastric and General Surgery, University Hospitals of Leicester, Leicester LE5 4PW, UK; Ahmed.ahmed@doctors.org.uk
7 Pharmacy Practice Research Unit, Clinical Pharmacy Department, College of Pharmacy, Jazan University, Jazan 45142, Saudi Arabia; ssalqahtani@jazanu.edu.sa
8 Department of Medical Laboratories Sciences, College of Applied Medical Sciences, Najran University, Najran 66446, Saudi Arabia; asmezher@nu.edu.sa
9 Department of Pharmacology, College of Pharmacy, King Khalid University, Abha 61421, Saudi Arabia; amsfr@kku.edu.sa
10 Department of Preventive Dental Sciences, Ibn Sina National College, Jeddah 22421, Saudi Arabia; amramadan@ibnsina.edu.sa
11 Department of Surgery, Faculty of Medicine Al-Neelain University, Khartoum 11111, Sudan
12 Faculty of Pharmacy, University of Khartoum, P. O. Box 321, Khartoum 11111, Sudan; Heyam57@hotmail.com
13 Institute of Endemic Diseases, University of Khartoum, Khartoum 11111, Sudan; mibrahim@iend.org
14 Scientific Direction, Foltra Medical Centre, 15886 Teo, Spain; jesus.devesa@usc.es
15 Department of Biosciences, Biotechnologies, and Biopharmaceutics, University of Bari, 70126 Bari, Italy; rosaangela.cardone@uniba.it (R.A.C.); stephanjoel.reshkin@uniba.it (S.J.R.)
16 Assistance Publique des Hôpitaux de Paris, 75003 Paris, France; dr.Laurentschwartz@gmail.com
* Correspondence: Alfarouk@hala-alfarouk.org; Tel.: +249-912-148-466

check for updates

Citation: Alfarouk, K.O.; AlHoufie, S.T.S.; Ahmed, S.B.M.; Shabana, M.; Ahmed, A.; Alqahtani, S.S.; Alqahtani, A.S.; Alqahtani, A.M.; Ramadan, A.M.; Ahmed, M.E.; et al. Pathogenesis and Management of COVID-19. *J. Xenobiot.* **2021**, *11*, 77–93. https://doi.org/10.3390/jox11020006

Academic Editor: Hernan Flores-Rozas

Received: 22 April 2021
Accepted: 12 May 2021
Published: 21 May 2021

Abstract: COVID-19, occurring due to SARS-COV-2 infection, is the most recent pandemic disease that has led to three million deaths at the time of writing. A great deal of effort has been directed towards altering the virus trajectory and/or managing the interactions of the virus with its subsequent targets in the human body; these interactions can lead to a chain reaction-like state manifested by a cytokine storm and progress to multiple organ failure. During cytokine storms the ratio of pro-inflammatory to anti-inflammatory mediators is generally increased, which contributes to the instigation of hyper-inflammation and confers advantages to the virus. Because cytokine expression patterns fluctuate from one person to another and even within the same person from one time to another, we suggest a road map of COVID-19 management using an individual approach instead of focusing on the blockbuster process (one treatment for most people, if not all). Here, we highlight the biology of the virus, study the interaction between the virus and humans, and present potential pharmacological and non-pharmacological modulators that might contribute to the global war against SARS-COV-2. We suggest an algorithmic roadmap to manage COVID-19.

Keywords: COVID-19; SARS-COV-2; virus; cytokine storm; pharmacology

1. Introduction

Deaths due to SARS-COV-2 infection have officially surpassed 3 million, with the probable number of victims being much higher. The latest surges of contagion are perhaps

stronger than the original wave and seem to be unstoppable. While vaccination is considered the best solution to eradicating the virus and halting the pandemic, the number of people vaccinated worldwide is very small, especially in the nations currently hardest hit, and probably will proceed very slowly. This leaves the health services that must save the lives of people already infected with few options at their disposal. The need is particularly critical given that the available evidence suggests the current treatment modalities have only a minimal impact on survival. Indeed, the significant variability in the clinical picture and outcomes in COVID-19 patients means that any single, comprehensive approach to treatment is a dead-end road. Further, our perceptions of COVID-19 and what we know of the virus, diagnosis, disease symptoms, course, treatment, and aftermath of its infection have changed with time.

If patients are to be treated with new possible therapeutic options, the basic biology of the infection process, especially the proteins and physiological conditions associated with the phases of the development of the disease, must be delineated to understand the challenges and tailor treatment to each individual. In this review, we highlight the biology of the virus, discuss the interaction between the virus and humans, and present an algorithmic roadmap of potential pharmacological and non-pharmacological modulators that might reduce the clinical effects of SARS-COV-2 infection. Adopting individualized medicine and pharmacodiagnostics might represent a more effective rationale, at least in severely ill patients.

2. Historical Preface

In 1930, a newly isolated virus strain caused acute respiratory infection in chickens, termed infectious bronchitis virus (IBV) [1,2]. Then, two additional animal viruses were isolated: In 1946, transmissible gastroenteritis virus (TGEV) affected pigs, and in 1949, mouse hepatitis virus (MHV) affected mice [3,4]. In the 1960s, the era of human coronaviruses started when David Tyrrell and ML Bynoe isolated a viral strain, called virus B814, from respiratory samples from a schoolboy with a common cold [5,6]. In the same decade, two additional species were isolated including human coronavirus 229E and human coronavirus organ culture 43 (HCoV-OC43) [7,8]. Almeida et al. called this group of viruses "coronavirus" as they resemble the "solar corona" or they are "in a crown" [9]. Feline infectious peritonitis virus in was isolated in 1963 [10], canine virus was isolated in 1971 [11,12], and porcine epidemic diarrhea virus (PEDV) was isolated in 1978 [13,14]. Finally, at the end of December 2019, three patients from the seafood and wet animal wholesale market in Wuhan, China were admitted to the hospital with pneumonia of unknown causes [15]. Later, Zhu et al. reported a novel beta-coronavirus, "CoV (2019-nCoV)," as the cause of this pneumonia. This novel virus was named "novel coronavirus-infected pneumonia" (NCIP), later known as SARS-COV-2, [15], and has evolved, consequently, into ten subtypes thus far [16] (See Figure 1).

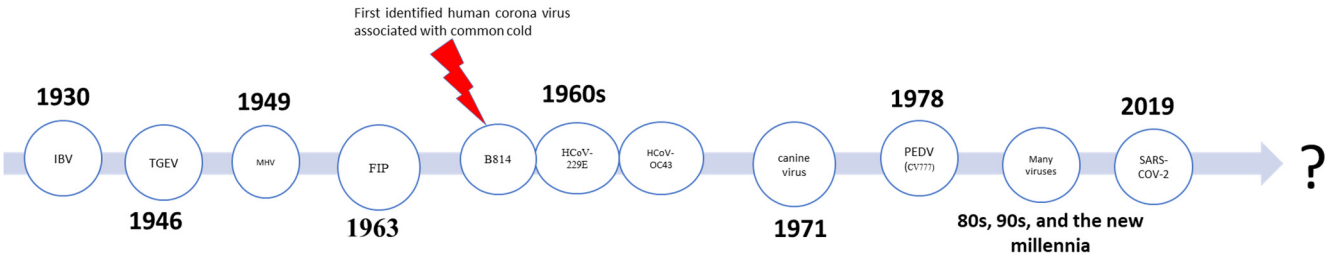

Figure 1. Summary of the timeline of discovery of many of coronavirus family members.

3. Virus Biology

The entry process depends on several factors, including virus-related factors (e.g., binding proteins) and host-related factors (e.g., tissue tropism or the tissue's ability to receive and accommodate the virus) [17]. The process of virus fusion and entry is more

complex, but, in general, it depends on acidification and/or proteolytic activation [18,19]; therefore, it is not surprising if systemic alkalization would be a rational approach to disrupt virus entry [20]. The fusion process occurs between the interaction of virus proteins and host receptor proteins. There are many viral proteins, one example being the S protein. The S protein is one of four structural proteins encoded by the CoV single-stranded, positive-sense RNA genome. In the viral membrane, the S protein functions to (i) interact with the cellular receptor and (ii) induce viral fusion with the cell via the plasma membrane protein angiotensin-converting enzyme 2 (ACE2) [21–24].

The S protein needs to be primed by an appropriate protease at the S1 and S2 interface (S1/S2) to catalyze the membrane fusion reaction and trigger the FPs immediately upstream (S2′). What is interesting about this triggering event is that several proteases can trigger it and it is the protease requirements that drive viral tropism.

Both SARS-CoV and MERS-CoV S can be triggered to fuse at either the plasma membrane or the endosomal membrane, and their route of access is determined by protease availability while being governed by the attachment of the surface unit, S1, of the S protein to a cellular receptor, facilitating viral attachment to a target cells' surface. Additionally, access involves S protein priming by cellular proteases, which involves S protein cleavage at the S1/S2 and the S2′ site and allows fusion of viral and cellular membranes, a process driven by the S2 subunit [25]. The SARS-COV-2 engages ACE2 as the entry receptor and employs the cellular serine protease TMPRSS2 for S protein priming [25].

Angiotensin-converting enzyme 2 (ACE2) receptors were shown to be the SARS-CoV-2 gateway to the cell [20–22]. ACE2 is an enzyme affixed to the plasma membrane (outer membrane) and is widely expressed among various human tissues. Expression levels differ from higher expression (small intestine, testis, kidneys, heart, thyroid, and adipose tissue), to medium expression (lungs, colon, liver, bladder, and adrenal gland), and to the lowest expression (blood, spleen, bone marrow, brain, blood vessels, and muscle) [26]. While lungs show medium expression compared to other tissues, SARS-COV-2 initially infects the lung [27]. However, we do not know whether the virus is disseminated to other parts of the body or not [21]. If yes, it will be of significant progress to know whether the multiple organ failure is associated with the side effect of drugs, ARDS, or with virus entry to that tissue [28–32].

After viral fusion with the plasma membrane, virus internalization can occur through various routes (Figure 2) [33–35]:

Non-endocytic pathway: This pathway could also be termed a "proteases-directed internalization pathway." After S protein binding to the receptor (not before), host proteases mediate virus–cell fusion [21,35,36]. Some of these proteases are trans-plasma membrane proteins. They play a crucial role in COVID-19. Some of these proteases include the following:

- Neutrophil elastase (NE): Elastase is a serine protease that also hydrolyzes amides. Neutrophil elastase is one of eight elastases found in the body. That NE could mediate entry is clinically vital since elastase is produced by neutrophils in the lungs during SARS-CoV-2 infection and could promote the progression of SARS-CoV-2 infection [16]. Therefore, as the hallmark of COVID-19, further neutrophils recruitment supports the release of a massive amount of NE and, subsequently, further virus entry [37–39] in a positive feedback cycle. Sivelestat is a NE inhibitor [40,41] and, so, might limit SARS-COV-2 entry. In this respect, we are not sure if the medications that decrease neutrophil counts will represent a potential treatment or not. Some of these medications include Carbimazole, Clozapine, Dapsone, Dipyrone, Methimazole, Penicillin G, Procainamide, Propylthiouracil, Rituximab, Sulfasalazine, and Ticlopidine;
- Type II transmembrane serine proteases, including transmembrane protease/serine subfamily member 2 (TMPRSS2) [42], also known as human epitheliasin [43]. Human TMPRSS2 mRNA is expressed in several tissues, including the prostate, ovary, breast, lung, kidney, pancreas, bile duct, salivary gland, stomach, small intestine, and

colon [43–45]. Transient expression of TMPRSS2 enhances SARS-CoV-2 S-mediated cell–cell fusion [21]. S protein is primed by TMPRSS2 and, therefore, TMPRSS2 supports virus entry, viral fusion, and spread and further increases the virus [46]. Nafamostat and Camostat are transmembrane protease inhibitors; serine 2 acts as a TMPRSS2 inhibitor [25,47–49]. Further, Nafamostast acts as an anticoagulant drug, which might shed light on how the virus induces thrombosis. Camostast is used for the treatment of pancreatitis. TMPRSS2 expression is subjected to population variability, e.g., TMPRSS2 expression is relatively lower in darker skin than in the white populations, suggesting that the probability of TMPRSS2-dependent virus internalization might be higher in a white population [50]. In addition, the expression of TMPRSS2 increases with aging [49], and TMPRSS2 expression is positively correlated with androgen levels, i.e., the male population [50].

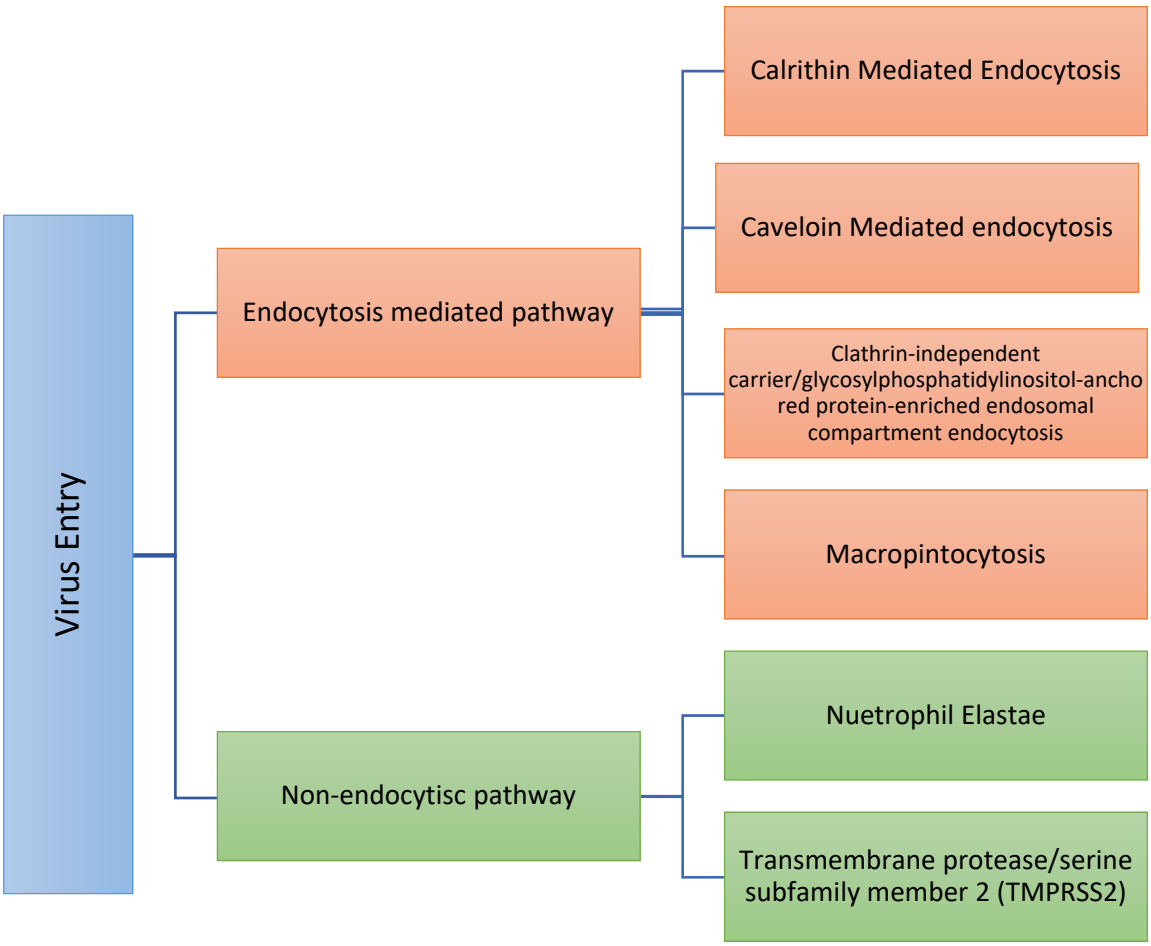

Figure 2. Summary of the different routes of virus entry. Therefore, proper determination of the exact route of entry might enhance the selection rationale for which targeted therapy should be used.

Although TMPRSS2 inhibition could be presented as a promising approach in managing SARS-COV-2 [25], we are not sure if blocking of TMPRSS2 will stop the viral infectivity or if the virus will adapt to such inhibition and undergo cellular internalization through another endocytic pathway, because if the plasma membrane-route proteases are available, the virus can fuse via an "early pathway" at the plasma membrane and, if not, the virus can fuse via a "late pathway" at the endosomal membrane [25].

The ***Endocytic pathway*** also could be termed as a receptor-mediated endocytosis pathway. The endocytosis pathway can be carried out through different routes, e.g., clathrin-mediated endocytosis, caveolin-mediated endocytosis, flotillin-dependent endocytosis, macropinocytosis, and clathrin-independent carrier/glycosylphosphatidylinositol-

anchored protein-enriched endosomal compartment endocytosis [33,51–55]. An acidic environment activates endosomal proteases such as cathepsin B and cathepsin L, which are known activators of other CoV family members, that become active in the early and late endosomes. To rationally target each approach, it will be wise to determine which route the virus follows to enter the cell endocytotically and then target it as follows.

- Clathrin-mediated endocytosis, the endosomal/lysosomal pathway, is the uptake of material (e.g., ferritin, LDL particles) into the cell from its surface using clathrin-coated vesicles [56], and the clathrin-coated vesicle changes its geometry to accommodate endocytosis [57,58]. Clathrin-mediated endocytosis can be inhibited by Pentamidine [20], dynasore [59], monodansylcadaverine (MDC) [20], depletion of intracellular potassium [20], phenylarside oxide (PAO) [60], cytosolic acidification (ammonium chloride (NH_4Cl)) [61], hypertonic shock (sucrose) [62], and chlorpromazine [63]. Importantly, in this respect, a group of French scientists observed a lower prevalence of symptomatic and severe forms of COVID-19 infections in psychiatric patients treated with the anti-psychotic drug chlorpromazine, and formulated the hypothesis that chlorpromazine might be a preventive against COVID-19 [20]. Following this observation, a clinical trial has been set-up [64].
- Caveolin-mediated endocytosis: Caveolae were described first in 1953 by Palade [65,66]. Caveolae and caveolin-containing membrane domains on the plasma membrane have various curvatures and shapes [66]. When the clathrin vesicles fuse with endosomes/lysosomes, the caveosome (multi-caveolar complexes) never fuses with lysosomes and, hence [67,68], it will not be surprising if SARS-COV-2 acts more through caveolin-mediated endocytosis [33] as that represents a successful anti-predator strategy. Vanadate, a tyrosine phosphatase inhibitor, stimulates caveolin-mediated endocytosis, while Nystatin (anti-fungal drug) suppresses the caveolin-mediated endocytosis, and chlorpromazine is non-specific [69]. Brefeldin A (antiviral drug) [70] and Nocodazole (anti-neoplastic drug) [71] also inhibit the caveolin pathway [72].
- Cathepsin B (catB): Cathepsin B is a lysosomal cysteine protease that belongs to the papain family [20,73]. Cathepsin B plays a vital role in intracellular proteolysis. In normal physiological conditions, active cathepsin B is localized to the endosomal/lysosomal compartment and is primarily involved in the normal turnover of intracellular and extracellular proteins, thus maintaining homeostatic metabolic activity within cells [71]. Beyond its effect in the mitochondrial complex I, metformin acts as a catB-inhibitor [73,74]. However, inhibition of catB will result in thyroid dysfunction, as catB is necessary for thyroxin production. Therefore, the targeting of catB should be cautiously monitored.
- Cathepsin L (catL): Cathepsin L can degrade nearly all proteins, including enzymes, receptors, and transcription factors [75]. The physiological function of catL depends on its subcellular localization as follows:
    - In endosomes/lysosomes: As it degrades the proteins in lysosomes, catL plays a crucial role in maintaining the lysosome–endosome compartment of the cardiac myocyte. Therefore, any alteration of catL might induce a progressive dilated cardiomyopathy [76–79]. In addition, disruption of catL might decrease CD+ T cells.
    - In the nucleus: Cathepsin L is a double-edged sword, it can either accelerate or inhibit the proliferation based on a couple of factors [75].
    - In the cytoplasm: Cathepsin L initiates the lysosomal pathways of apoptosis [80–82].
    - In the extracellular space: In the inflammatory environment, pro-inflammatory cytokines induce catL expression in endothelial cells, macrophages, and smooth muscle, then the released catL degrades elastin and collagen [75] and so might disrupt the matrix.

Cathepsin L has been identified as a highly effectual enzyme to degrade the viruses' outermost capsid and underlying proteins as a criterion to initiate an infection. The viruses access the endosomal–lysosomal compartment and thereafter disassemble by endocytosis. The subvirion particles penetrate to the cytoplasm to replicate [75,83]. Therefore, catL plays a critical role in the entry of the SARS-COV-2 virus [84]. Cathepsin L inhibitors such as CTLA-2α [85], the selective N-(benzyloxycarbonyl)-L-phenylalanyl-L-tyrosinal [86], MDL28170 [87], and even slight alkalization show a gradual reduction in fusion due to catL activity [87].

4. Cytokine Storm

It seems that the first introduction of the term cytokine storm was used in early 1993 to describe the role of interleukin 1 on graft-versus-host disease [88]. Cytokine storm might be a synonym to immune attack or massive immune response against foreign bodies, e.g., bacteria [89] and viruses [90–92], where SARS-COV-2 is one of those viruses. However, the cytokine storm in COVID-19 surely does not develop directly as an immune response to the virus [93,94] nor as a result of the multiple organ failure [95] due to COVID-19 [93]. A cytokine profile resembling systemic lupus erythematosus (SLE) and/or secondary hemophagocytic lymphohistiocytosis (sHLH), is associated with COVID-19 disease severity and is characterized by an increase in the following:

Interleukin 1 beta (IL-1β), also termed lymphocyte activating factor, leukocytic pyrogen, leukocytic endogenous mediator, or mononuclear cell factor is a pro-protein converted to mature IL-1β by cytosolic caspase 1 [96] and produced by activated macrophages [97]. IL-1β plays a crucial role in mediating autoimmunity [98]. The monoclonal anti-IL-1β antibody, canakinumab, is a suggested inhibitor [99,100]. In this regard, Novartis started a clinical trial to show the effect of Canakinumab against COVID-19 [101]. Curcumin also shows an inhibitory effect on IL-1 [102].

Granulocyte-colony stimulating factor (G-CSF) is a secreted glycoprotein produced by macrophages, endothelial cells, stromal cells, natural killer cells, and T cells [103]. There are four types of CSF: granulocyte-colony stimulating factor, macrophage-colony stimulating factor, granulocyte-macrophage-colony stimulating factor, and multi-colony stimulating factor (interleukin-3) [104]. G-CSF supports production and differentiation of white blood cells. G-CSF supports neutrophil proliferation, and GM-CSF supports macrophages and eosinophils proliferation [105]. Administration of G-CSF is associated with increased lactate dehydrogenase, uric acid, isoenzymes, alkaline phosphatase, and the increase in soluble IL-2 receptors [104], which are found at higher levels in serum of COVID-19 patients [106–109]. G-CSF plasma levels were also correlated with the severity of COVID-19 (higher in patients in the intensive care unit) [110–112]. Therefore, targeting the G-CSF/G-CSF receptor axis to manage COVID-19 should be considered.

Interferon-gamma-inducible protein-10 (IP-10)/CXCL10, also called IP-10, is a small protein chemokine (10kDa) induced by IFN- γ and produced by many cell types, e.g., neutrophils, monocytes, endothelial cells, fibroblasts, and keratinocytes. Physiologically, CXCL10 recruits natural killer cells (NK cells), eosinophils, and leukocytes and increases the Th1/Th2 ratio [113–115]. CXCL10 also increases the level of several inflammatory mediators, including TNF-α that promotes inflammation. Therefore, CXCL10 is considered an inflammatory chemokine that contributes to many autoimmune diseases [113,116,117]. The CXCL levels increase 10-fold in COVID-19 and they play a paramount role in its immunopathology [118,119]. CXCL10 inhibition might represent a rational approach to the target, and its inhibitors include Vitamin D [120], Thiazolidinediones [121], Ganodermycin [120], and artemether combined with atorvastatin [120,122,123], although the earlier data about the last example suggested the reverse effect.

Macrophage inflammatory protein 1-α (MIP 1-α) belongs to the family of chemokines, also known as MIP-1alpha chemokine (C-C motif) ligand 3 (CCL3) [124]. Upon activation, they can be expressed by hematopoietic cells and a variety of tissue cells such as fibroblasts, epithelial cells, vascular smooth muscle cells, or platelets [125,126]. MCP 1-α

are best known for their chemotactic and pro-inflammatory effects and are crucial for immune responses towards infection and inflammation and are produced by countless cells, particularly macrophages, dendritic cells, and lymphocytes [127]. MIP 1-α is associated with COVID-19 [128,129] and, therefore, targeting MIP 1-α directly or altering it at the receptor level (CCL3 blocker) represents a wise approach to managing COVID-19 [130]. IL-10 inhibits MIP 1-α expression [131].

Monocyte chemoattractant protein 1(MCP-1/CCL2) is also known as the small inducible cytokine A2. Although monocyte/macrophages are the primary sources of CCL2, many cells also produce MCP1, such as endothelial, epithelial, smooth muscle, fibroblasts, mesangial, astrocytic, monocytic, and microglial cells [132–135]. Those cells are responsible for antiviral immunity. Many factors stimulate MCP-1 production, such as oxidative stress, growth factors, and cytokines. MCP-1 is the critical regulator of migration and infiltration of monocytes and macrophages [132]. MCP1 recruits monocytes, dendritic cells, and T-cells (memory) to the inflammation site because of inflammation and infection [136]. MCP-1 is subject to population variability as it is higher in whiter skin than in darker skin populations [137,138]. MCP-1 is associated with COVID-19 [139–141]; therefore, targeting MCP-1 could also be considered in managing SARS-2 infection [130]. Melatonin inhibits MCP-1 expression [142]. Bindarit decreases MCP-1 synthesis [143]. Spiegelmer (L-enantiomeric RNA oligonucleotide mNOX-E36), also called L-ribonucleic acid aptamer, inhibits MCP-1 activity [144]. Furthermore, MCP-1 could be blocked at the receptor level (CCR2 blockage) [143] using compounds such as 747 (a natural combination related in structure to kaempferol) [145] and 15a (an orthostatic CCR2, a small molecule antagonist) [146].

Tumor necrosis factor-α (TNF-α) is also called cachexin or cachectin. TNF-α is a cell-signaling protein produced mainly by macrophages in response to stimuli and mediates the inflammatory response [147–149]. A great deal of data showed that TNF-α has a receptor association with COVID-19 and higher TNF-α expression is correlated with disease severity and higher mortality [150–153]. It is not surprising that anti-TNF-α drugs (adalimumab (A), certolizumab pegol (C), etanercept (E), golimumab (G), and infliximab (I)) are considered anti-COVID-19 treatments [152–157] (Table 1).

Table 1. Cytokines/chemokines that mediate the cytokine storm, with their antagonists.

The Cytokine/Chemokine	Possible Antagonist
Interleukin 1 beta (IL-1β)	Canakinumab [99,100]
Interferon-γ inducible protein 10 (CXCL10)	Vitamin D, Thiazolidinediones, Ganodermycin [120,121]
Monocyte chemoattractant protein 1(MCP-1/CCL2)	Bindarit, Spiegelmer, compounds such as 747, 15a [143–146]
Macrophage inflammatory protein 1-α (MIP 1-α)	CCL3 blocker, IL-10 [130,131]
Tumor necrosis factor-α (TNF-α)	Adalimumab (A), certolizumab pegol (C), etanercept (E), golimumab (G), and infliximab (I) [154]

5. Notes on Some Currently Administered Pharmacological Modulating Agents

Administration off-label of certain drugs (drug repurposing) that target the virus and/or the cytokine storm has become a promising approach in managing COVID-19 [158]; some of these agents include:

Macrolide antibiotics: These antibiotics inhibit bacterial protein synthesis. Therefore, they are clinically used to fight infections by atypical bacterial (bacteria that lack cell walls). Evidence shows their promising activity in the management of COVID-19 [159].

-Azithromycin exerts its immunomodulatory role via the following:

(i) Suppression of LPS-induced MDC and IP-10 expression through the MAPK–JNK and the NFκB–p65 pathways [160];

(ii) Inhibition of the cytoplasmic phospholipase A_2, so it might be equivalent to steroids that suppress the release of eicosanoids (prostaglandins, thromboxane, leukotrienes, and HEPTE) [161].

-Clarithromycin is another macrolide antibiotic that is useful in the management of COVID-19 due to its following properties:

- Influence on two steps in the influenza virus entry process. The drug was found to reduce the expression of sialic acid residues on the surface of airway epithelial cells, reduce virus binding, and reduce the number of acidic endosomes in the cell, inhibiting endosomal escape [34];
- Alteration of endosomal pH. Clarithromycin also inhibits the release of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) [162] and might support the mortality rate due to SARS-COV-2 [163]. The massive release of cytokines in such conditions raises another possible question: Does the cytokine storm support the viral entry and dissemination across the body or is the cytokine storm just a consequence of massive uncontrolled cell death?
- Stabilization of the mast cells [164]. Mast cells secret both histamine and heparin. Therefore, clarithromycin might prevent the massive release of histamine and prevent anaphylaxis and perhaps the blood coagulation that might result from activation of factor XII through the bradykinin activation. However, the prevailing medical dogma is that heparin is an anticoagulant.

Although macrolides have proven useful in their administration as anti-COVID-19 drugs by attenuating the cytokine storm, they exert additional benefits in the management of patients with COVID-19 by reducing the incidence of bacterial co-infection [165].

Amiloride: Amiloride is a well-known potassium-sparing diuretic. It has been shown to inhibit micropinocytosis [69], which might alter this viral entry pathway. It also inhibits the E protein, which is crucial for viral replication [166].

Sodium bicarbonate: Spike proteins of SARS-COV-2 become more disordered at alkaline pH values while becoming more well-formed at more acidic pH values. Therefore, increasing extracellular pH most probably alters the ACE2–SARS-COV-2 interaction dynamics [167]. Hence, sodium bicarbonate used as a buffer has been suggested as it attenuates the hyper-inflammatory environment [168]. In this respect, potassium citrate as a buffer might also be beneficial in COVID-19 treatment [169].

6. Food Supplements That Might Prevent COVID-19 Complications

There are some food supplements that might prevent or decrease the severity of COVID-19 infection; some of these food supplements include:

N-Acetyl Cysteine (NAC): NAC is a precursor of glutathione used to treat paracetamol overdoses and is a mucolytic (loosens thick mucus in the lungs). NAC is an immune booster and an anti-inflammatory and antiviral agent. Therefore, it is a suitable agent for COVD-19 [170], significantly reducing the cytokine storm [171]. NAC has also been used in the management of critically ill septic patients [170].

Vitamin E has a lysosomal membrane stabilization function [172,173] and has an inhibitory effect on the production of several pro-inflammatory cytokines, including IL-1, IL-6, TNF, and the chemokine IL-8, by monocytes and macrophages. Vitamin E can also stimulate the intracellular type I IFN system, which exercises antiviral activities [174]. Therefore, it might be beneficial in prevention and/or management of COVID-19 complications.

Desferrioxamine is an iron-chelating agent. A higher level of transferrin indicates a higher level of iron, which is toxic in humans. Blocking receptor-mediated endocytosis reduced the internalization of some infectious viruses similarly to the reduction of endocytosis by transferrin [175], suggesting that transferrin might be an indicator of how viruses enter the cells and how some possible inhibitors could function by inducing paralysis of receptor-mediated endocytosis, e.g., amiloride and NH4Cl [176]. In this respect, desferrioxamine might show potential activity as an anti-COVID-19 treatment [177].

Zinc is an essential trace element found in humans, plants, and microorganisms. Nearly 10% of human proteins (enzymes, transcriptional factors, etc.) bind with zinc. In plasma, 60% of zinc is bound with albumin and around 10% with transferrin (iron transporter, see above). Thus, if iron is increased, free zinc is reduced (hypozincemia) [178,179]. In COVID-19, the

level of iron is increased significantly, and, therefore, the level of free zinc is reduced, and this is associated with poor outcomes [180–182]. Thus, a zinc supplement is a wise choice in the management of COVID-19 [183].

Vitamin C is a known antioxidant and its role in treating sepsis has been reported [184, 185], which supports the notion that vitamin C could be considered in COVID-19 treatment [186]. A clinical trial involving 140 patients will be conducted in Wuhan, China. The scientists will be assessing the need for the ventilator, vasopressors, organ failure, the length of ICU stay, and the mortality in response to high doses of vitamin C [187].

Vitamin K With the increasing evidence that microthrombi formation is linked to COVID 19 infection [188,189], low molecular weight heparin, Fondaparinux, oral anticoagulants, or vitamin K antagonists have been recommended to all patients with an active infection unless they have a relevant contraindication [190–193], therefore, the level of vitamin K should be closely adjusted.

Vitamin D (calcitriol), although it is one of the fat-soluble vitamins, it is considered to be a hormone [194,195]. As a hormone, vitamin D activates innate immunity and suppresses adaptive immunity [196,197]. Vitamin D deficiency is also associated with viral infection and is accompanied by acute respiratory distress syndrome [197,198]. Therefore, many trials have been carried to test it against COVID-19.

Melatonin is a hormone mainly secreted from the pineal gland [199]. Melatonin is an enormously powerful antioxidant hormone. Melatonin inhibits the activation of the primary inflammasome NLRP3, which leads to cytokine storms [200]. Besides its activity in the antioxidant cascade [201–204], melatonin supports the expression of many antioxidant cellular enzymes, including glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase [205,206]. As some of these enzymes are mitochondrial enzymes, melatonin is also a mitochondrial antioxidant [207,208] and, thus, it can be used to manage COVID-19 [209,210].

7. Roadmap to Manage COVID-19 and Concluding Remarks

COVID-19 is an emerging pandemic disease threatening human life. COVID-19 manifests as hyper-inflammation and heterogenous increases or decreases in cytokines, chemokines, electrolytes imbalance, etc. The significant variability in the clinical picture and outcomes in COVID-19 patients means that any blockbuster approach to treatment is a dead-end road. Adopting individualized medicine and pharmacodiagnostics (predictive medicine) might represent a more effective rationale, at least in severely ill patients [211,212].

Prevention by implementing facemask usage is important; some public health practitioners and theoreticians are raising the possibility of herd immunity, but that comes at a high cost of more deaths [213]. This roadmap for optimizing decision making to tailor and fine-tune therapy to the characteristics of the disease and specific needs of the patient includes (i) managing the infection via its signs and symptoms (e.g., cytokine, hyper-inflammation) and prevention of co-infection by targeting the virus and/or the cytokine storm to avoid co-infection, whether bacterial, viral, or by other microorganisms; and (ii) delaying the post-infection toxicity, e.g., thromboembolism. Moreover, the administration of pharmacological and/or nutraceutical compounds that support the repairing of the injured lung epithelium, especially among older people, will represent a promising strategy in the war against COVID-19.

Author Contributions: K.O.A. contributed to the conceptualization, data curation, formal analysis, investigation, resources, software, and writing (original draft). L.S. and S.J.R. contributed to the supervision, conceptualization, data curation, formal analysis, investigation, resources, software, and writing (review and editing). S.T.S.A., S.B.M.A. and M.S. contributed to the conceptualization, data curation, resources, and writing (original draft). A.A., S.S.A., A.S.A., A.M.A., A.M.R., M.E.A. and H.S.A. contributed to methodology, resources, and software. A.B., J.D., R.A.C. and M.E.I. contributed to the investigation, methodology, and visualization. S.J.R. and L.S. contributed to investigation, methodology, and resources. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Estola, T. Coronaviruses, a new group of animal RNA viruses. *Avian Dis.* **1970**, *14*, 330–336. [CrossRef] [PubMed]
2. Schalk, A.; Hawn, M. An apparently new respiratory disease of baby chicks. *J. Am. Vet. Med. Assoc.* **1931**, *78*, 413–422.
3. McIntosh, K. Coronaviruses: A Comparative Review. In *Current Topics in Microbiology and Immunology/Ergebnisse der Mikrobiologie und Immunitätsforschung*; Springer: Berlin/Heidelberg, Germany, 1974; pp. 85–129.
4. Fenner, F.; Bachmann, P.; Gibbs, E.; Murphy, F.; Studdert, M.; White, D. Coronaviridae. In *Veterinary Virology*; Elsevier: Amsterdam, The Netherlands, 1987; pp. 505–518.
5. Tyrrell, D.A.J.; Bynoe, M.L. Cultivation of a Novel Type of Common-cold Virus in Organ Cultures. *Br. Med. J.* **1965**, *1*, 1467–1470. [CrossRef] [PubMed]
6. Tyrrell, D.A.J. Hunting Common Cold Viruses by Some New Methods. *J. Infect. Dis.* **1970**, *121*, 561–571. [CrossRef] [PubMed]
7. Kahn, J.S.; McIntosh, K. History and Recent Advances in Coronavirus Discovery. *Pediatr. Infect. Dis. J.* **2005**, *24*, S223–S227. [CrossRef]
8. Geller, C.; Varbanov, M.; Duval, R.E. Human coronaviruses: Insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses* **2012**, *4*, 3044–3068. [CrossRef]
9. Virology: Coronaviruses. *Nature* **1968**, *220*, 650. [CrossRef]
10. Pedersen, N.C. A review of feline infectious peritonitis virus infection: 1963–2008. *J. Feline Med. Surg.* **2009**, *11*, 225–258. [CrossRef] [PubMed]
11. Binn, L.N.; Lazar, E.C.; Keenan, K.P.; Huxsoll, D.L.; Marchwicki, R.H.; Strano, A.J. Recovery and characterization of a coronavirus from military dogs with diarrhea. *Proc. Annu. Meet. U. S. Anim. Health Assoc.* **1974**, 359–366.
12. Pratelli, A. The evolutionary processes of canine coronaviruses. *Adv. Virol.* **2011**, *2011*, 562831. [CrossRef]
13. Pensaert, M.B.; de Bouck, P. A new coronavirus-like particle associated with diarrhea in swine. *Arch. Virol.* **1978**, *58*, 243–247. [CrossRef] [PubMed]
14. Yang, D.K.; Kim, H.H.; Lee, S.H.; Yoon, S.S.; Park, J.W.; Cho, I.S. Isolation and characterization of a new porcine epidemic diarrhea virus variant that occurred in Korea in 2014. *J. Vet. Sci.* **2018**, *19*, 71–78. [CrossRef]
15. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.* **2020**, *382*, 727–733. [CrossRef] [PubMed]
16. Bhattacharyya, C.; Das, C.; Ghosh, A.; Singh, A.K.; Mukherjee, S.; Majumder, P.P.; Basu, A.; Biswas, N.K. Global Spread of SARS-CoV-2 Subtype with Spike Protein Mutation D614G is Shaped by Human Genomic Variations that Regulate Expression of TMPRSS2 and MX1 Genes. *bioRxiv* **2020**. [CrossRef]
17. Baron, S.; Fons, M.; Albrecht, T. Viral Pathogenesis. In *Medical Microbiology*; Baron, S., Ed.; Elsevier Ltd.: Galveston, TX, USA, 1996; ISBN 9780123744104.
18. Belouzard, S.; Millet, J.K.; Licitra, B.N.; Whittaker, G.R. Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses* **2012**, *4*, 1011–1033. [CrossRef] [PubMed]
19. Chu, V.C.; McElroy, L.J.; Chu, V.; Bauman, B.E.; Whittaker, G.R. The Avian Coronavirus Infectious Bronchitis Virus Undergoes Direct Low-pH-Dependent Fusion Activation during Entry into Host Cells. *J. Virol.* **2006**, *80*, 3180–3188. [CrossRef]
20. Moore, L.L.; Bostick, D.A.; Garry, R.F. Sindbis virus infection decreases intracellular pH: Alkaline medium inhibits processing of sindbis virus polyproteins. *Virology* **1988**, *166*, 1–9. [CrossRef]
21. Tang, T.; Bidon, M.; Jaimes, J.A.; Whittaker, G.R.; Daniel, S. Coronavirus membrane fusion mechanism offers a potential target for antiviral development. *Antivir. Res.* **2020**, *178*, 104792. [CrossRef]
22. Yan, R.; Zhang, Y.; Li, Y.; Xia, L.; Guo, Y.; Zhou, Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* **2020**, *367*, 1444–1448. [CrossRef]
23. Li, W.; Moore, M.J.; Vasllieva, N.; Sui, J.; Wong, S.K.; Berne, M.A.; Somasundaran, M.; Sullivan, J.L.; Luzuriaga, K.; Greeneugh, T.C.; et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* **2003**, *426*, 450–454. [CrossRef]
24. Zhou, P.; Yang, X.L.; Wang, X.G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.R.; Zhu, Y.; Li, B.; Huang, C.L.; et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **2020**, *579*, 270–273. [CrossRef] [PubMed]
25. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Mü, M.A.; Drosten, C.; Pö, S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271–280.e8. [CrossRef] [PubMed]
26. Li, M.-Y.; Li, L.; Zhang, Y.; Wang, X.-S. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect. Dis. Poverty* **2020**, *9*, 45. [CrossRef] [PubMed]
27. Li, H.; Liu, S.M.; Yu, X.H.; Tang, S.L.; Tang, C.K. Coronavirus disease 2019 (COVID-19): Current status and future perspectives. *Int. J. Antimicrob. Agents* **2020**, *55*, 105951. [CrossRef]

28. Diao, B.; Feng, Z.; Wang, C.; Wang, H.; Liu, L.; Wang, C.; Wang, R.; Liu, Y.; Liu, Y.; Wang, G.; et al. Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. *medRxiv* **2020**, *2*. [CrossRef]
29. Maisch, B. SARS-CoV-2 as potential cause of cardiac inflammation and heart failure. Is it the virus, hyperinflammation, or MODS? *Herz* **2020**, *45*, 321–322. [CrossRef] [PubMed]
30. Wang, W.; Xu, Y.; Gao, R.; Lu, R.; Han, K.; Wu, G.; Tan, W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* **2020**, *323*, 1843–1844. [CrossRef]
31. Brancatella, A.; Ricci, D.; Viola, N.; Sgrò, D.; Santini, F.; Latrofa, F. Subacute Thyroiditis After Sars-COV-2 Infection. *J. Clin. Endocrinol. Metab.* **2020**, *105*, 2367–2370. [CrossRef] [PubMed]
32. Wei, L.; Sun, S.; Xu, C.-H.; Zhang, J.; Xu, Y.; Zhu, H.; Peh, S.-C.; Korteweg, C.; McNutt, M.A.; Gu, J. Pathology of the thyroid in severe acute respiratory syndrome. *Hum. Pathol.* **2007**, *38*, 95–102. [CrossRef]
33. Wang, H.; Yang, P.; Liu, K.; Guo, F.; Zhang, Y.; Zhang, G.; Jiang, C. SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. *Cell Res.* **2008**, *18*, 290–301. [CrossRef]
34. Thorley, J.A.; McKeating, J.A.; Rappoport, J.Z. Mechanisms of viral entry: Sneaking in the front door. *Protoplasma* **2010**, *244*, 15–24. [CrossRef]
35. Zumla, A.; Chan, J.F.W.; Azhar, E.I.; Hui, D.S.C.; Yuen, K.-Y. Coronaviruses—Drug discovery and therapeutic options. *Nat. Rev. Drug Discov.* **2016**, *15*, 327–347. [CrossRef] [PubMed]
36. Belouzard, S.; Madu, I.; Whittaker, G.R. Elastase-mediated activation of the severe acute respiratory syndrome coronavirus spike protein at discrete sites within the S2 domain. *J. Biol. Chem.* **2010**, *285*, 22758–22763. [CrossRef]
37. Zuo, Y.; Yalavarthi, S.; Shi, H.; Gockman, K.; Zuo, M.; Madison, J.A.; Blair, C.N.; Weber, A.; Barnes, B.J.; Egeblad, M.; et al. Neutrophil extracellular traps in COVID-19. *JCI Insight* **2020**. [CrossRef]
38. Liu, Y.; Du, X.; Chen, J.; Jin, Y.; Peng, L.; Wang, H.H.X.; Luo, M.; Chen, L.; Zhao, Y. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J. Infect.* **2020**, *81*, e6–e12. [CrossRef] [PubMed]
39. Lagunas-Rangel, F.A. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *J. Med. Virol.* **2020**, *92*, 1733–1734. [CrossRef]
40. Benabid, R.; Wartelle, J.; Malleret, L.; Guyot, N.; Gangloff, S.; Lebargy, F.; Belaaouaj, A. Neutrophil elastase modulates cytokine expression: Contribution to host defense against pseudomonas aeruginosa-induced pneumonia. *J. Biol. Chem.* **2012**, *287*, 34883–34894. [CrossRef]
41. Ono, S.; Kuroki, T.; Adachi, T.; Kosaka, T.; Okamoto, T.; Tanaka, T.; Tajima, Y.; Kanematsu, T.; Eguchi, S. The effect of selective neutrophil elastase inhibitor on pancreatic islet yields and functions in rat with hypercytokinemia. *Ann. Transplant.* **2011**, *16*, 99–106. [CrossRef]
42. Antalis, T.M.; Bugge, T.H.; Wu, Q. Membrane-anchored serine proteases in health and disease. In *Progress in Molecular Biology and Translational Science*; Elsevier B.V.: Amsterdam, The Netherlands, 2011; Volume 99, pp. 1–50.
43. Paoloni-Giacobino, A.; Chen, H.; Peitsch, M.C.; Rossier, C.; Antonarakis, S.E. Cloning of the TMPRSS2 gene, which encodes a novel serine protease with transmembrane, LDLRA, and SRCR domains and maps to 21q22.3. *Genomics* **1997**, *44*, 309–320. [CrossRef]
44. Jacquinet, E.; Rao, N.V.; Rao, G.V.; Hoidal, J.R. Cloning, genomic organization, chromosomal assignment and expression of a novel mosaic serine proteinase: Epitheliasin. *FEBS Lett.* **2000**, *468*, 93–100. [CrossRef]
45. Lin, B.; Ferguson, C.; White, J.T.; Wang, S.; Vessella, R.; True, L.D.; Hood, L.; Nelson, P.S. Prostate-localized and androgen-regulated expression of the membrane- bound serine protease TMPRSS2. *Cancer Res.* **1999**, *59*, 4180–4184. [PubMed]
46. Matsuyama, S.; Nao, N.; Shirato, K.; Kawase, M.; Saito, S.; Takayama, I.; Nagata, N.; Sekizuka, T.; Katoh, H.; Kato, F.; et al. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 7001–7003. [CrossRef] [PubMed]
47. Kawase, M.; Shirato, K.; van der Hoek, L.; Taguchi, F.; Matsuyama, S. Simultaneous Treatment of Human Bronchial Epithelial Cells with Serine and Cysteine Protease Inhibitors Prevents Severe Acute Respiratory Syndrome Coronavirus Entry. *J. Virol.* **2012**, *86*, 6537–6545. [CrossRef]
48. Zhou, Y.; Vedantham, P.; Lu, K.; Agudelo, J.; Carrion, R.; Nunneley, J.W.; Barnard, D.; Pöhlmann, S.; McKerrow, J.H.; Renslo, A.R.; et al. Protease inhibitors targeting coronavirus and filovirus entry. *Antivir. Res.* **2015**, *116*, 76–84. [CrossRef]
49. Rensi, S.; Altman, R.B.; Liu, T.; Lo, Y.-C.; McInnes, G.; Derry, A.; Keys, A. Homology Modeling of TMPRSS2 Yields Candidate Drugs That May Inhibit Entry of SARS-CoV-2 into Human Cells. *ChemRxiv* **2020**. [CrossRef]
50. Schuler, B.A.; Christian Habermann, A.; Plosa, E.J.; Taylor, C.J.; Jetter, C.; Kapp, M.E.; Benjamin, J.T.; Gulleman, P.; Nichols, D.S.; Braunstein, L.Z.; et al. Age-related expression of SARS-CoV-2 priming protease TMPRSS2 in the developing lung. *bioRxiv* **2020**. [CrossRef]
51. Inoue, Y.; Tanaka, N.; Tanaka, Y.; Inoue, S.; Morita, K.; Zhuang, M.; Hattori, T.; Sugamura, K. Clathrin-Dependent Entry of Severe Acute Respiratory Syndrome Coronavirus into Target Cells Expressing ACE2 with the Cytoplasmic Tail Deleted. *J. Virol.* **2007**, *81*, 8722–8729. [CrossRef]
52. Doherty, G.J.; McMahon, H.T. Mechanisms of Endocytosis. *Annu. Rev. Biochem.* **2009**, *78*, 857–902. [CrossRef]
53. Burkard, C.; Verheije, M.H.; Wicht, O.; van Kasteren, S.I.; van Kuppeveld, F.J.; Haagmans, B.L.; Pelkmans, L.; Rottier, P.J.M.; Bosch, B.J.; de Haan, C.A.M. Coronavirus Cell Entry Occurs through the Endo-/Lysosomal Pathway in a Proteolysis-Dependent Manner. *PLoS Pathog.* **2014**, *10*, e1004502. [CrossRef]

54. Fekri, F.; Abousawan, J.; Bautista, S.; Orofiamma, L.; Dayam, R.M.; Antonescu, C.N.; Karshafian, R. Targeted enhancement of flotillin-dependent endocytosis augments cellular uptake and impact of cytotoxic drugs. *Sci. Rep.* **2019**, *9*, 17768. [CrossRef]
55. Glebov, O.O. Understanding SARS-CoV-2 endocytosis for COVID-19 drug repurposing. *FEBS J.* **2020**, *287*, 3664–3671. [CrossRef]
56. McMahon, H.T.; Boucrot, E. Molecular mechanism and physiological functions of clathrin-mediated endocytosis. *Nat. Rev. Mol. Cell Biol.* **2011**, *12*, 517–533. [CrossRef]
57. Rust, M.J.; Lakadamyali, M.; Zhang, F.; Zhuang, X. Assembly of endocytic machinery around individual influenza viruses during viral entry. *Nat. Struct. Mol. Biol.* **2004**, *11*, 567–573. [CrossRef]
58. Ehrlich, M.; Boll, W.; Van Oijen, A.; Hariharan, R.; Chandran, K.; Nibert, M.L.; Kirchhausen, T. Endocytosis by random initiation and stabilization of clathrin-coated pits. *Cell* **2004**, *118*, 591–605. [CrossRef] [PubMed]
59. Macia, E.; Ehrlich, M.; Massol, R.; Boucrot, E.; Brunner, C.; Kirchhausen, T. Dynasore, a Cell-Permeable Inhibitor of Dynamin. *Dev. Cell* **2006**, *10*, 839–850. [CrossRef]
60. Gibson, A.E.; Noel, R.J.; Herlihy, J.T.; Ward, W.F. Phenylarsine oxide inhibition of endocytosis: Effects on asialofetuin internalization. *Am. J. Physiol. Cell Physiol.* **1989**, *257*, C182–C184. [CrossRef] [PubMed]
61. Cosson, P.; De Curtis, I.; Pouyssegur, J.; Griffiths, G.; Davoust, J. Low cytoplasmic pH inhibits endocytosis and transport from the trans-Golgi network to the cell surface. *J. Cell Biol.* **1989**, *108*, 377–387. [CrossRef]
62. Heuser, J.E.; Anderson, R.G.W. Hypertonic media inhibit receptor-mediated endocytosis by blocking clathrin-coated pit formation. *J. Cell Biol.* **1989**, *108*, 389–400. [CrossRef] [PubMed]
63. Wang, L.H.; Rothberg, K.G.; Anderson, R.G.W. Mis-assembly of clathrin lattices on endosomes reveals a regulatory switch for coated pit formation. *J. Cell Biol.* **1993**, *123*, 1107–1117. [CrossRef] [PubMed]
64. Plaze, M.; Attali, D.; Petit, A.-C.; Blatzer, M.; Simon-Loriere, E.; Vinckier, F.; Cachia, A.; Chrétien, F.; Gaillard, R. Repurposing chlorpromazine to treat COVID-19: The reCoVery study. *Encephale* **2020**, *46*, 169–172. [CrossRef] [PubMed]
65. Palade, G.E. PROGRAM. Proceedings of the Electron Microscope Society of America. *J. Appl. Phys.* **1953**, *24*, 1414–1425. [CrossRef]
66. Kiss, A.L.; Botos, E. Endocytosis via caveolae: Alternative pathway with distinct cellular compartments to avoid lysosomal degradation? *J. Cell. Mol. Med.* **2009**, *13*, 1228–1237. [CrossRef] [PubMed]
67. Pelkmans, L.; Kartenbeck, J.; Helenius, A. Caveolar endocytosis of simian virus 40 reveals a new two-step vesicular-transport pathway to the ER. *Nat. Cell Biol.* **2001**, *3*, 473–483. [CrossRef]
68. Nichols, B.J. A distinct class of endosome mediates clathrin-independent endocytosis to the Golgi complex. *Nat. Cell Biol.* **2002**, *4*, 374–378. [CrossRef]
69. Nunes-Correia, I.; Eulálio, A.; Nir, S.; Pedroso de Lima, M.C. Caveolae as an additional route for influenza virus endocytosis in MDCK cells. *Cell. Mol. Biol. Lett.* **2004**, *9*, 47–60. [PubMed]
70. Tamura, G.; Ando, K.; Suzuki, S.; Takatsuki, A.; Arima, K. Antiviral activity of brefeldin A and verrucarin A. *J. Antibiot.* **1968**, *21*, 160–161. [CrossRef]
71. Beswick, R.W.; Ambrose, H.E.; Wagner, S.D. Nocodazole, a microtubule depolymerising agent, induces apoptosis of chronic lymphocytic leukaemia cells associated with changes in Bcl-2 phosphorylation and expression. *Leuk. Res.* **2006**, *30*, 427–436. [CrossRef]
72. Le, P.U.; Nabi, I.R. Distinct caveolae-mediated endocytic pathways target the Golgi apparatus and the endoplasmic reticulum. *J. Cell Sci.* **2003**, *116*, 1059–1071. [CrossRef] [PubMed]
73. Gobec, S.; Frlan, R. Inhibitors of Cathepsin B. *Curr. Med. Chem.* **2006**, *13*, 2309–2327. [CrossRef]
74. Sweeney, D.; Raymer, M.L.; Lockwood, T.D. Antidiabetic and antimalarial biguanide drugs are metal-interactive antiproteolytic agents. *Biochem. Pharmacol.* **2003**, *66*, 663–677. [CrossRef]
75. Kirschke, H.; Cathepsin, L. *Handbook of Proteolytic Enzymes*; Elsevier Ltd.: Amsterdam, The Netherlands, 2013; Volume 2, pp. 1808–1817, ISBN 9780123822192.
76. Spira, D.; Stypmann, J.; Tobin, D.J.; Petermann, I.; Mayer, C.; Hagemann, S.; Vasiljeva, O.; Günther, T.; Schüle, R.; Peters, C.; et al. Cell type-specific functions of the lysosomal protease cathepsin L in the heart. *J. Biol. Chem.* **2007**, *282*, 37045–37052. [CrossRef]
77. Petermann, I.; Mayer, C.; Stypmann, J.; Biniossek, M.L.; Tobin, D.J.; Engelen, M.A.; Dandekar, T.; Grune, T.; Schild, L.; Peters, C.; et al. Lysosomal, cytoskeletal, and metabolic alterations in cardiomyopathy of cathepsin L knockout mice. *FASEB J.* **2006**, *20*, 1266–1268. [CrossRef]
78. Stypmann, J.; Gläser, K.; Roth, W.; Tobin, D.J.; Petermann, I.; Matthias, R.; Mönnig, G.; Haverkamp, W.; Breithardt, G.; Schmahl, W.; et al. Dilated cardiomyopathy in mice deficient for the lysosomal cysteine peptidase cathepsin L. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 6234–6239. [CrossRef]
79. Tang, Q.; Cai, J.; Shen, D.; Bian, Z.; Yan, L.; Wang, Y.X.; Lan, J.; Zhuang, G.Q.; Ma, W.Z.; Wang, W. Lysosomal cysteine peptidase cathepsin L protects against cardiac hypertrophy through blocking AKT/GSK3β signaling. *J. Mol. Med.* **2009**, *87*, 249–260. [CrossRef] [PubMed]
80. Chwieralski, C.E.; Welte, T.; Bühling, F. Cathepsin-regulated apoptosis. *Apoptosis* **2006**, *11*, 143–149. [CrossRef]
81. Fogarty, M.P.; McCormack, R.M.; Noonan, J.; Murphy, D.; Gowran, A.; Campbell, V.A. A role for p53 in the Beta-amyloid-mediated regulation of the lysosomal system. *Neurobiol. Aging* **2010**, *31*, 1774–1786. [CrossRef] [PubMed]
82. Kaasik, A.; Rikk, T.; Piirsoo, A.; Zharkovsky, T.; Zharkovsky, A. Up-regulation of lysosomal cathepsin L and autophagy during neuronal death induced by reduced serum and potassium. *Eur. J. Neurosci.* **2005**, *22*, 1023–1031. [CrossRef]

83. Huang, I.C.; Bosch, B.J.; Li, F.; Li, W.; Kyoung, H.L.; Ghiran, S.; Vasilieva, N.; Dermody, T.S.; Harrison, S.C.; Dormitzer, P.R.; et al. SARS coronavirus, but not human coronavirus NL63, utilizes cathepsin L to infect ACE2-expressing cells. *J. Biol. Chem.* **2006**, *281*, 3198–3203. [CrossRef]
84. Ou, X.; Liu, Y.; Lei, X.; Li, P.; Mi, D.; Ren, L.; Guo, L.; Guo, R.; Chen, T.; Hu, J.; et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat. Commun.* **2020**, *11*, 1620. [CrossRef] [PubMed]
85. Sugita, S.; Horie, S.; Nakamura, O.; Maruyama, K.; Takase, H.; Usui, Y.; Takeuchi, M.; Ishidoh, K.; Koike, M.; Uchiyama, Y.; et al. Acquisition of T Regulatory Function in Cathepsin L-Inhibited T Cells by Eye-Derived CTLA-2α during Inflammatory Conditions. *J. Immunol.* **2009**, *183*, 5013–5022. [CrossRef] [PubMed]
86. Woo, J.T.; Yamaguchi, K.; Hayama, T.; Kobori, T.; Sigeizumi, S.; Sugimoto, K.; Kondo, K.; Tsuji, T.; Ohba, Y.; Tagami, K.; et al. Suppressive effect of N-(benzyloxycarbonyl)-L-phenylalanyl-L-tyrosinal on bone resorption in vitro and in vivo. *Eur. J. Pharmacol.* **1996**, *300*, 131–135. [CrossRef]
87. Simmons, G.; Gosalia, D.N.; Rennekamp, A.J.; Reeves, J.D.; Diamond, S.L.; Bates, P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11876–11881. [CrossRef]
88. Ferrara, J.L.M.; Abhyankar, S.; Gilliland, D.G. Cytokine storm of graft-versus-host disease: A critical effector role for interleukin-1. *Transplant. Proc.* **1993**, *25*, 1216–1217.
89. Bisno, A.L.; Brito, M.O.; Collins, C.M. Molecular basis of group A streptococcal virulence. *Lancet Infect. Dis.* **2003**, *3*, 191–200. [CrossRef]
90. Yokota, S. Influenza-associated Encephalopathy–Pathophysiology and Disease Mechanisms. *Nihon Rinsho Jpn. J. Clin. Med.* **2003**, *61*, 1953–1958.
91. Jahrling, P.B.; Hensley, L.E.; Martinez, M.J.; LeDuc, J.W.; Rubins, K.H.; Relman, D.A.; Huggins, J.W. Exploring the potential of variola virus infection of cynomolgus macaques as a model for human smallpox. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 15196–15200. [CrossRef] [PubMed]
92. Huang, K.J.; Su, I.J.; Theron, M.; Wu, Y.C.; Lai, S.K.; Liu, C.C.; Lei, H.Y. An interferon-γ-related cytokine storm in SARS patients. *J. Med. Virol.* **2005**, *75*, 185–194. [CrossRef]
93. Mehta, P.; McAuley, D.F.; Brown, M.; Sanchez, E.; Tattersall, R.S.; Manson, J.J. COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet* **2020**, *395*, 1033–1034. [CrossRef]
94. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* **2020**, *395*, 1054–1062. [CrossRef]
95. Wang, H.; Ma, S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. *Am. J. Emerg. Med.* **2008**, *26*, 711–715. [CrossRef]
96. Denes, A.; Lopez-Castejon, G.; Brough, D. Caspase-1: Is IL-1 just the tip of the ICEberg? *Cell Death Dis.* **2012**, *3*, e338. [CrossRef] [PubMed]
97. Beuscher, H.U.; Günther, C.; Röllinghoff, M. IL-1 beta is secreted by activated murine macrophages as biologically inactive precursor. *J. Immunol.* **1990**, *144*, 2179–2183. [PubMed]
98. Sutton, C.E.; Lalor, S.J.; Sweeney, C.M.; Brereton, C.F.; Lavelle, E.C.; Mills, K.H.G. Interleukin-1 and IL-23 Induce Innate IL-17 Production from γδ T Cells, Amplifying Th17 Responses and Autoimmunity. *Immunity* **2009**, *31*, 331–341. [CrossRef]
99. Dhimolea, E. Canakinumab. *MAbs* **2010**, *2*, 3–13. [CrossRef] [PubMed]
100. Dinarello, C.A.; Simon, A.; van der Meer, J.W.M. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat. Rev. Drug Discov.* **2012**, *11*, 633–652. [CrossRef]
101. Sheng, C.C.; Sahoo, D.; Dugar, S.; Prada, R.A.; Wang, T.K.M.; Abou Hassan, O.K.; Brennan, D.; Culver, D.A.; Rajendram, P.; Duggal, A.; et al. Canakinumab to reduce deterioration of cardiac and respiratory function in SARS-CoV-2 associated myocardial injury with heightened inflammation (canakinumab in Covid-19 cardiac injury: The three C study). *Clin. Cardiol.* **2020**, *43*, 1055–1063. [CrossRef] [PubMed]
102. Sun, J.; Zhao, Y.; Hu, J. Curcumin Inhibits Imiquimod-Induced Psoriasis-Like Inflammation by Inhibiting IL-1beta and IL-6 Production in Mice. *PLoS ONE* **2013**, *8*, e67078. [CrossRef]
103. Alsina, M.; Guise, T.A.; Roodman, G.D. Cytokine Regulation of Bone Cell Differentiation. In *Vitamins and Hormones*; Academic Press Inc.: Cambridge, MA, USA, 1996; Volume 52, pp. 63–98.
104. Wood, A.J.; Lieschke, G.J.; Burgess, A.W. Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor. *N. Engl. J. Med.* **1992**, *327*, 28–35. [CrossRef]
105. Root, R.K.; Dale, D.C. Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor: Comparisons and Potential for Use in the Treatment of Infections in Nonneutropenic Patients. *J. Infect. Dis.* **1999**, *179*, S342–S352. [CrossRef]
106. Yan, L.; Zhang, H.-T.; Goncalves, J.; Xiao, Y.; Wang, M.; Guo, Y.; Sun, C.; Tang, X.; Jing, L.; Zhang, M.; et al. An interpretable mortality prediction model for COVID-19 patients. *Nat. Mach. Intell.* **2020**, *2*, 283–288. [CrossRef]
107. Cai, Q.; Huang, D.; Yu, H.; Zhu, Z.; Xia, Z.; Su, Y.; Li, Z.; Zhou, G.; Gou, J.; Qu, J.; et al. COVID-19: Abnormal liver function tests. *J. Hepatol.* **2020**, *73*, 566–574. [CrossRef]
108. Han, H.; Ma, Q.; Li, C.; Liu, R.; Zhao, L.; Wang, W.; Zhang, P.; Liu, X.; Gao, G.; Liu, F.; et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg. Microbes Infect.* **2020**, *9*, 1123–1130. [CrossRef]

109. Filardi, T.; Morano, S. COVID-19: Is there a link between the course of infection and pharmacological agents in diabetes? *J. Endocrinol. Investig.* **2020**, *43*, 1053–1060. [CrossRef]
110. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497–506. [CrossRef]
111. Velavan, T.P.; Meyer, C.G. Mild versus severe COVID-19: Laboratory markers. *Int. J. Infect. Dis.* **2020**, *95*, 304–307. [CrossRef]
112. Malek, A.E. Time to revisit the use of G-CSF after allogeneic haematopoietic cell transplantation in COVID-19 era? *Br. J. Cancer* **2021**, *124*, 1183. [CrossRef]
113. Lee, E.Y.; Lee, Z.-H.; Song, Y.W. CXCL10 and autoimmune diseases. *Autoimmun. Rev.* **2009**, *8*, 379–383. [CrossRef]
114. Zhao, Q.; Kim, T.; Pang, J.; Sun, W.; Yang, X.; Wang, J.; Song, Y.; Zhang, H.; Sun, H.; Rangan, V.; et al. A novel function of CXCL10 in mediating monocyte production of proinflammatory cytokines. *J. Leukoc. Biol.* **2017**, *102*, 1271–1280. [CrossRef]
115. Ohta, K.; Naruse, T.; Kato, H.; Ishida, Y.; Nakagawa, T.; Ono, S.; Shigeishi, H.; Takechi, M. Differential regulation by IFN-γ on TNF-α-induced chemokine expression in synovial fibroblasts from temporomandibular joint. *Mol. Med. Rep.* **2017**, *16*, 6850–6857. [CrossRef]
116. Vazirinejad, R.; Ahmadi, Z.; Kazemi Arababadi, M.; Hassanshahi, G.; Kennedy, D. The Biological Functions, Structure and Sources of CXCL10 and Its Outstanding Part in the Pathophysiology of Multiple Sclerosis. *Neuroimmunomodulation* **2014**, *21*, 322–330. [CrossRef]
117. Qi, X.F.; Kim, D.H.; Yoon, Y.S.; Jin, D.; Huang, X.Z.; Li, J.H.; Deung, Y.K.; Lee, K.J. Essential involvement of cross-talk between IFN-γ and TNF-α in CXCL10 production in human THP-1 monocytes. *J. Cell. Physiol.* **2009**, *220*, 690–697. [CrossRef]
118. Vaninov, N. In the eye of the COVID-19 cytokine storm. *Nat. Rev. Immunol.* **2020**, *20*, 277. [CrossRef]
119. Coperchini, F.; Chiovato, L.; Croce, L.; Magri, F.; Rotondi, M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev.* **2020**, *53*, 25. [CrossRef]
120. Jung, M.; Liermann, J.C.; Opatz, T.; Erkel, G. Ganodermycin, a novel inhibitor of CXCL10 expression from Ganoderma applanatum. *J. Antibiot.* **2011**, *64*, 683–686. [CrossRef] [PubMed]
121. Seidel, P.; Alkhouri, H.; Lalor, D.J.; Burgess, J.K.; Armour, C.L.; Hughes, J.M. Thiazolidinediones inhibit airway smooth muscle release of the chemokine CXCL10: In vitro comparison with current asthma therapies. *Respir. Res.* **2012**, *13*, 90. [CrossRef] [PubMed]
122. Castiglione, V.; Chiriacò, M.; Emdin, M.; Taddei, S.; Vergaro, G. Statin therapy in COVID-19 infection. *Eur. Heart J. Cardiovasc. Pharmacother.* **2020**, *6*, 258–259. [CrossRef]
123. Lee, K.C.H.; Sewa, D.W.; Phua, G.C. Potential role of statins in COVID-19. *Int. J. Infect. Dis.* **2020**, *96*, 615–617. [CrossRef]
124. Zlotnik, A.; Yoshie, O. Chemokines: A new classification system and their role in immunity. *Immunity* **2000**, *1*, 121–127. [CrossRef]
125. Menten, P.; Wuyts, A.; Van Damme, J. Macrophage inflammatory protein-1. *Cytokine Growth Factor Rev.* **2002**, *13*, 455–481. [CrossRef]
126. Ren, M.; Guo, Q.; Guo, L.; Lenz, M.; Qian, F.; Koenen, R.R.; Xu, H.; Schilling, A.B.; Weber, C.; Ye, R.D.; et al. Polymerization of MIP-1 chemokine (CCL3 and CCL4) and clearance of MIP-1 by insulin-degrading enzyme. *EMBO J.* **2010**, *29*, 3952–3966. [CrossRef] [PubMed]
127. Maurer, M.; von Stebut, E. Macrophage inflammatory protein-1. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 1882–1886. [CrossRef]
128. Xu, Z.-S.; Shu, T.; Kang, L.; Wu, D.; Zhou, X.; Liao, B.-W.; Sun, X.-L.; Zhou, X.; Wang, Y.-Y. Temporal profiling of plasma cytokines, chemokines and growth factors from mild, severe and fatal COVID-19 patients. *Signal Transduct. Target. Ther.* **2020**, *5*, 100. [CrossRef] [PubMed]
129. Tufan, A.; Avanoğlu Güler, A.; Matucci-Cerinic, M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. *Turk. J. Med. Sci.* **2020**, *50*, 620–632. [CrossRef] [PubMed]
130. Lu, L.; Zhang, H.; Zhan, M.; Jiang, J.; Yin, H.; Dauphars, D.J.; Li, S.-Y.; Li, Y.; He, Y.-W. Preventing Mortality in COVID-19 Patients: Which Cytokine to Target in a Raging Storm? *Front. Cell Dev. Biol.* **2020**, *8*, 677. [CrossRef]
131. Berkman, N.; John, M.; Roesems, G.; Jose, P.J.; Barnes, P.J.; Chung, K.F. Inhibition of macrophage inflammatory protein-1 alpha expression by IL-10. Differential sensitivities in human blood monocytes and alveolar macrophages. *J. Immunol.* **1995**, *155*, 4412–4418.
132. Barna, B.P.; Pettay, J.; Barnett, G.H.; Zhou, P.; Iwasaki, K.; Estes, M.L. Regulation of monocyte chemoattractant protein-1 expression in adult human non-neoplastic astrocytes is sensitive to tumor necrosis factor (TNF) or antibody to the 55-kDa TNF receptor. *J. Neuroimmunol.* **1994**, *50*, 101–107. [CrossRef]
133. Brown, Z.; Strieter, R.M.; Neild, G.H.; Thompson, R.C.; Kunkel, S.L.; Westwick, J. IL-1 receptor antagonist inhibits monocyte chemotactic peptide 1 generation by human mesangial cells. *Kidney Int.* **1992**, *42*, 95–101. [CrossRef] [PubMed]
134. Cushing, S.D.; Berliner, J.A.; Valente, A.J.; Territo, M.C.; Navab, M.; Parhami, F.; Gerrity, R.; Schwartz, C.J.; Fogelman, A.M. Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 5134–5138. [CrossRef]
135. Standiford, T.J.; Kunkel, S.L.; Phan, S.H.; Rollins, B.J.; Strieter, R.M. Alveolar macrophage-derived cytokines induce monocyte chemoattractant protein-1 expression from human pulmonary type II-like epithelial cells. *J. Biol. Chem.* **1991**, *266*, 9912–9918. [CrossRef]

136. Lu, B.; Rutledge, B.J.; Gu, L.; Fiorillo, J.; Lukacs, N.W.; Kunkel, S.L.; North, R.; Gerard, C.; Rollins, B.J. Abnormalities in monocyte recruitment and cytokine expression in monocyte chemoattractant protein 1-deficient mice. *J. Exp. Med.* **1998**, *187*, 601–608. [CrossRef]
137. Bielinski, S.J.; Pankow, J.S.; Miller, M.B.; Hopkins, P.N.; Eckfeldt, J.H.; Hixson, J.; Liu, Y.; Register, T.; Myers, R.H.; Arnett, D.K. Circulating MCP-1 levels shows linkage to chemokine receptor gene cluster on chromosome 3: The NHLBI Family Heart Study follow-up examination. *Genes Immun.* **2007**, *8*, 684–690. [CrossRef]
138. Dupuis, J.; Larson, M.G.; Vasan, R.S.; Massaro, J.M.; Wilson, P.W.F.; Lipinska, I.; Corey, D.; Vita, J.A.; Keaney, J.F.; Benjamin, E.J. Genome scan of systemic biomarkers of vascular inflammation in the Framingham Heart Study: Evidence for susceptibility loci on 1q. *Atherosclerosis* **2005**, *182*, 307–314. [CrossRef] [PubMed]
139. Costela-Ruiz, V.J.; Illescas-Montes, R.; Puerta-Puerta, J.M.; Ruiz, C.; Melguizo-Rodríguez, L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev.* **2020**, *54*, 62–75. [CrossRef]
140. Hussman, J.P. Cellular and Molecular Pathways of COVID-19 and Potential Points of Therapeutic Intervention. *Front. Pharmacol.* **2020**, *11*, 1169. [CrossRef] [PubMed]
141. Yang, Y.; Shen, C.; Li, J.; Yuan, J.; Wei, J.; Huang, F.; Wang, F.; Li, G.; Li, Y.; Xing, L.; et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *J. Allergy Clin. Immunol.* **2020**, *146*, 119–127. [CrossRef]
142. Yu, G.M.; Tan, W. Melatonin Inhibits Lipopolysaccharide-Induced Inflammation and Oxidative Stress in Cultured Mouse Mammary Tissue. *Mediat. Inflamm.* **2019**, *2019*. [CrossRef] [PubMed]
143. Das, A.; Yan, L. Anti-CCL-2/MCP-1: Directed biologicals for inflammatory and malignant diseases. In *Target Validation in Drug Discovery*; Elsevier Inc.: Amsterdam, The Netherlands, 2007; pp. 103–119, ISBN 9780123693938.
144. Baeck, C.; Wehr, A.; Karlmark, K.R.; Heymann, F.; Vucur, M.; Gassler, N.; Huss, S.; Klussmann, S.; Eulberg, D.; Luedde, T.; et al. Pharmacological inhibition of the chemokine CCL2 (MCP-1) diminishes liver macrophage infiltration and steatohepatitis in chronic hepatic injury. *Gut* **2012**, *61*, 416–426. [CrossRef]
145. Yao, W.; Ba, Q.; Li, X.; Li, H.; Zhang, S.; Yuan, Y.; Wang, F.; Duan, X.; Li, J.; Zhang, W.; et al. A Natural CCR2 Antagonist Relieves Tumor-associated Macrophage-mediated Immunosuppression to Produce a Therapeutic Effect for Liver Cancer. *EBioMedicine* **2017**, *22*, 58–67. [CrossRef]
146. Bot, I.; Zacarías, N.V.O.; De Witte, W.E.A.; De Vries, H.; Van Santbrink, P.J.; Van Der Velden, D.; Kröner, M.J.; Van Der Berg, D.J.; Stamos, D.; De Lange, E.C.M.; et al. A novel CCR2 antagonist inhibits atherogenesis in apoE deficient mice by achieving high receptor occupancy. *Sci. Rep.* **2017**, *7*, 52. [CrossRef]
147. Parameswaran, N.; Patial, S. Tumor necrosis factor-α signaling in macrophages. *Crit. Rev. Eukaryot. Gene Expr.* **2010**, *20*, 87–103. [CrossRef]
148. Gahring, L.C.; Carlson, N.G.; Kulmer, R.A.; Rogers, S.W. Neuronal expression of tumor necrosis factor alpha in the OVOUJI fme brain. *Neuroimmunomodulation* **1996**, *3*, 289–303. [CrossRef] [PubMed]
149. Kale, V.P.; Gilhooley, P.J.; Phadtare, S.; Nabavizadeh, A.; Pandey, M.K. Role of Gambogic Acid in Chemosensitization of Cancer. In *Role of Nutraceuticals in Chemoresistance to Cancer*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 151–167.
150. Mortaz, E.; Tabarsi, P.; Jamaati, H.; Roofchayee, N.D.; Dezfuli, N.K.; Hashemian, S.M.; Moniri, A.; Marjani, M.; Malkmohammad, M.; Mansouri, D.; et al. Increased serum levels of soluble TNF-α receptor is associated with mortality of ICU COVID-19 patients. *Front. Immunol.* **2020**. [CrossRef]
151. Brito, C.A.; Paiva, J.G.; Pimentel, F.N.; Guimarães, R.S.; Moreira, M.R. COVID-19 in patients with rheumatological diseases treated with anti-TNF. *Ann. Rheum. Dis.* **2020**. [CrossRef]
152. Perlin, D.S.; Zafir-Lavie, I.; Roadcap, L.; Raines, S.; Ware, C.F.; Neil, G.A. Levels of the TNF-Related Cytokine LIGHT Increase in Hospitalized COVID-19 Patients with Cytokine Release Syndrome and ARDS. *mSphere* **2020**, *5*. [CrossRef] [PubMed]
153. Feldmann, M.; Maini, R.N.; Woody, J.N.; Holgate, S.T.; Winter, G.; Rowland, M.; Richards, D.; Hussell, T. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet* **2020**, *395*, 1407–1409. [CrossRef]
154. Gerriets, V.; Bansal, P.; Goyal, A.; Khaddour, K. *Tumor Necrosis Factor Inhibitors*; StatPearls Publishing: Treasure Island, FL, USA, 2021.
155. Robinson, P.C.; Richards, D.; Tanner, H.L.; Feldmann, M. Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment. *Lancet Rheumatol.* **2020**, *2*, e653–e655. [CrossRef]
156. Duret, P.-M.; Sebbag, E.; Mallick, A.; Gravier, S.; Spielmann, L.; Messer, L. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. *Ann. Rheum. Dis.* **2020**, *79*, 1251–1252. [CrossRef]
157. Stallmach, A.; Kortgen, A.; Gonnert, F.; Coldewey, S.M.; Reuken, P.; Bauer, M. Infliximab against severe COVID-19-induced cytokine storm syndrome with organ failure-a cautionary case series. *Crit. Care* **2020**, *24*, 444. [CrossRef]
158. Buonaguro, F.M.; Ascierto, P.A.; Morse, G.D.; Buonaguro, L.; Puzanov, I.; Tornesello, M.L.; Bréchot, C.; Gallo, R.C. Covid-19: Time for a paradigm change. *Rev. Med. Virol.* **2020**, *30*, e2134. [CrossRef]
159. Pani, A.; Lauriola, M.; Romandini, A.; Scaglione, F. Macrolides and viral infections: Focus on azithromycin in COVID-19 pathology. *Int. J. Antimicrob. Agents* **2020**, *56*, 106053. [CrossRef]
160. Kuo, C.H.; Lee, M.S.; Kuo, H.F.; Lin, Y.C.; Hung, C.H. Azithromycin suppresses Th1- and Th2-related chemokines IP-10/MDC in human monocytic cell line. *J. Microbiol. Immunol. Infect.* **2019**, *52*, 872–879. [CrossRef]
161. Banjanac, M.; Munić Kos, V.; Nujić, K.; Vrančić, M.; Belamarić, D.; Crnković, S.; Hlevnjak, M.; Eraković Haber, V. Anti-inflammatory mechanism of action of azithromycin in LPS-stimulated J774A.1 cells. *Pharmacol. Res.* **2012**, *66*, 357–362. [CrossRef]

162. Yamaya, M.; Shinya, K.; Hatachi, Y.; Kubo, H.; Asada, M.; Yasuda, H.; Nishimura, H.; Nagatomi, R. Clarithromycin inhibits type A seasonal influenza virus infection in human airway epithelial cells. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 81–90. [CrossRef]
163. Huang, J.; Hume, A.J.; Abo, K.M.; Werder, R.B.; Villacorta-Martin, C.; Alysandratos, K.D.; Beermann, M.L.; Simone-Roach, C.; Lindstrom-Vautrin, J.; Olejnik, J.; et al. SARS-CoV-2 Infection of Pluripotent Stem Cell-Derived Human Lung Alveolar Type 2 Cells Elicits a Rapid Epithelial-Intrinsic Inflammatory Response. *Cell Stem Cell* **2020**. [CrossRef]
164. Kazama, I.; Saito, K.; Baba, A.; Mori, T.; Abe, N.; Endo, Y.; Toyama, H.; Ejima, Y.; Matsubara, M.; Yamauchi, M. Clarithromycin Dose-Dependently Stabilizes Rat Peritoneal Mast Cells. *Chemotherapy* **2016**, *61*, 295–303. [CrossRef]
165. Sterenczak, K.A.; Barrantes, I.; Stahnke, T.; Stachs, O.; Fuellen, G.; Undre, N. Co-infections: Testing macrolides for added benefit in patients with COVID-19. *Lancet Microbe* **2020**, *1*, e313. [CrossRef]
166. Wilson, L.; Gage, P.; Ewart, G. Hexamethylene amiloride blocks E protein ion channels and inhibits coronavirus replication. *Virology* **2006**, *353*, 294–306. [CrossRef] [PubMed]
167. Zhou, T.; Tsybovsky, Y.; Olia, A.S.; Gorman, J.; Rapp, M.A.; Cerutti, G.; Katsamba, P.S.; Nazzari, A.; Schon, A.; Wang, P.D.; et al. A pH-dependent switch mediates conformational masking of SARS-CoV-2 spike. *bioRxiv* **2020**. [CrossRef]
168. Ray, S.C.; Baban, B.; Tucker, M.A.; Seaton, A.J.; Chang, K.C.; Mannon, E.C.; Sun, J.; Patel, B.; Wilson, K.; Musall, J.B.; et al. Oral $NaHCO_3$ Activates a Splenic Anti-Inflammatory Pathway: Evidence That Cholinergic Signals Are Transmitted via Mesothelial Cells. *J. Immunol.* **2018**, *200*, 3568–3586. [CrossRef]
169. Vlachakis, D.; Papakonstantinou, E.; Mitsis, T.; Pierouli, K.; Diakou, I.; Chrousos, G.; Bacopoulou, F. Molecular mechanisms of the novel coronavirus SARS-CoV-2 and potential anti-COVID19 pharmacological targets since the outbreak of the pandemic. *Food Chem. Toxicol.* **2020**, *146*, 111805. [CrossRef]
170. Shi, Z.; Puyo, C.A. N-acetylcysteine to combat COVID-19: An evidence review. *Ther. Clin. Risk Manag.* **2020**, *16*, 1047–1055. [CrossRef]
171. Assimakopoulos, S.F.; Marangos, M. N-acetyl-cysteine may prevent COVID-19-associated cytokine storm and acute respiratory distress syndrome. *Med. Hypotheses* **2020**, *140*, 109778. [CrossRef]
172. Bulger, E.M.; Maier, R.V. An Argument for Vitamin E Supplementation in the Management of Systemic Inflammatory Response Syndrome. *Shock* **2003**, *19*, 99–103. [CrossRef]
173. Mukherjee, A.K.; Ghosal, S.K.; Maity, C.R. Lysosomal membrane stabilization by α-tocopherol against the damaging action of Vipera russelli venom phospholipase A2. *Cell. Mol. Life Sci.* **1997**, *53*, 152–155. [CrossRef]
174. Fiorino, S.; Gallo, C.; Zippi, M.; Sabbatani, S.; Manfredi, R.; Moretti, R.; Fogacci, E.; Maggioli, C.; Travasoni Loffredo, F.; Giampieri, E.; et al. Cytokine storm in aged people with CoV-2: Possible role of vitamins as therapy or preventive strategy. *Aging Clin. Exp. Res.* **2020**, *32*, 2115–2131. [CrossRef]
175. Wessling-Resnick, M. Crossing the Iron Gate: Why and How Transferrin Receptors Mediate Viral Entry. *Annu. Rev. Nutr.* **2018**, *38*, 431–458. [CrossRef]
176. Varga, M.J.; Weibull, C.; Everitt, E. Infectious entry pathway of adenovirus type 2. *J. Virol.* **1991**, *65*, 6061. [CrossRef] [PubMed]
177. Dalamaga, M.; Karampela, I.; Mantzoros, C.S. Commentary: Could iron chelators prove to be useful as an adjunct to COVID-19 Treatment Regimens? *Metabolism* **2020**, *108*, 154260. [CrossRef] [PubMed]
178. Banach, W.; Nitschke, K.; Krajewska, N.; Mongiałło, W.; Matuszak, O.; Muszyński, J.; Skrypnik, D. The Association between Excess Body Mass and Disturbances in Somatic Mineral Levels. *Int. J. Mol. Sci.* **2020**, *21*, 7306. [CrossRef]
179. Delima, R.; Trinder, D.; Olynyk, J.K. Potential protective effects of zinc in iron overload. *Liver Int.* **2007**, *27*, 4–5. [CrossRef] [PubMed]
180. Jothimani, D.; Kailasam, E.; Danielraj, S.; Nallathambi, B.; Ramachandran, H.; Sekar, P.; Manoharan, S.; Ramani, V.; Narasimhan, G.; Kaliamoorthy, I.; et al. COVID-19: Poor outcomes in patients with zinc deficiency. *Int. J. Infect. Dis.* **2020**, *100*, 343–349. [CrossRef]
181. Djoko, K.Y.; Cheryl-lynn, Y.O.; Walker, M.J.; McEwan, A.G. The role of copper and zinc toxicity in innate immune defense against bacterial pathogens. *J. Biol. Chem.* **2015**, *290*, 1854–1861. [CrossRef]
182. Rink, L.; Gabriel, P. Zinc and the immune system. *Proc. Nutr. Soc.* **2000**, *59*, 541–552. [CrossRef] [PubMed]
183. Pal, A.; Squitti, R.; Picozza, M.; Pawar, A.; Rongioletti, M.; Dutta, A.K.; Sahoo, S.; Goswami, K.; Sharma, P.; Prasad, R. Zinc and COVID-19: Basis of Current Clinical Trials. *Biol. Trace Elem. Res.* **2020**, 1–11. [CrossRef]
184. Marik, P.E.; Khangoora, V.; Rivera, R.; Hooper, M.H.; Catravas, J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. *Chest* **2017**, *151*, 1229–1238. [CrossRef]
185. Litwak, J.; Cho, N.; Nguyen, H.; Moussavi, K.; Bushell, T. Vitamin C, Hydrocortisone, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Analysis of Real-World Application. *J. Clin. Med.* **2019**, *8*, 478. [CrossRef]
186. Feyaerts, A.F.; Luyten, W. Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19? *Nutrition* **2020**, *79–80*, 110948. [CrossRef]
187. Carr, A.C. A new clinical trial to test high-dose vitamin C in patients with COVID-19. *Crit. Care* **2020**, *24*, 133. [CrossRef]
188. Ahmed, S.; Zimba, O.; Gasparyan, A.Y. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. *Clin. Rheumatol.* **2020**, *39*, 2529–2543. [CrossRef]
189. Loo, J.; Spittle, D.A.; Newnham, M. COVID-19, immunothrombosis and venous thromboembolism: Biological mechanisms. *Thorax* **2021**, *76*, 412–420. [CrossRef]

190. Marongiu, F.; Barcellona, D. Fondaparinux: Should It Be Studied in Patients with COVID-19 Disease? *TH Open* **2020**, *4*, e300–e302. [CrossRef]
191. Cuker, A.; Tseng, E.K.; Nieuwlaat, R.; Angchaisuksiri, P.; Blair, C.; Dane, K.; Davila, J.; DeSancho, M.T.; Diuguid, D.; Griffin, D.O.; et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv.* **2021**, *5*, 872–888. [CrossRef]
192. Bikdeli, B.; Madhavan, M.V.; Gupta, A.; Jimenez, D.; Burton, J.R.; Der Nigoghossian, C.; Chuich, T.; Nouri, S.N.; Dreyfus, I.; Driggin, E.; et al. Pharmacological Agents Targeting Thromboinflammation in COVID-19: Review and Implications for Future Research. *Thromb. Haemost.* **2020**, *120*, 1004–1024.
193. Russo, V.; Cardillo, G.; Viggiano, G.V.; Mangiacapra, S.; Cavalli, A.; Fontanella, A.; Agrusta, F.; Bellizzi, A.; Amitrano, M.; Iannuzzo, M.; et al. Fondaparinux Use in Patients With COVID-19: A Preliminary Multicenter Real-World Experience. *J. Cardiovasc. Pharmacol.* **2020**, *76*, 369–371. [CrossRef]
194. Demer, L.L.; Hsu, J.J.; Tintut, Y. Steroid Hormone Vitamin D: Implications for Cardiovascular Disease. *Circ. Res.* **2018**, *122*, 1576–1585. [CrossRef] [PubMed]
195. Norman, A.W. From vitamin D to hormone D: Fundamentals of the vitamin D endocrine system essential for good health. *Am. J. Clin. Nutr.* **2008**, *88*, 491S–499S. [CrossRef]
196. Hewison, M. Vitamin D and innate and adaptive immunity. *Vitam. Horm.* **2011**, *86*, 23–62. [CrossRef]
197. Bishop, E.L.; Ismailova, A.; Dimeloe, S.; Hewison, M.; White, J.H. Vitamin D and Immune Regulation: Antibacterial, Antiviral, Anti-Inflammatory. *JBMR Plus* **2021**, *5*. [CrossRef]
198. Quesada-Gomez, J.M.; Entrenas-Castillo, M.; Bouillon, R. Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections: Revised Ms SBMB 2020_166. *J. Steroid Biochem. Mol. Biol.* **2020**, *202*. [CrossRef] [PubMed]
199. Aulinas, A. *Physiology of the Pineal Gland and Melatonin*; MDText.com, Inc.: 2000.
200. Zhang, R.; Wang, X.; Ni, L.; Di, X.; Ma, B.; Niu, S.; Liu, C.; Reiter, R.J. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci.* **2020**, *250*, 117583. [CrossRef]
201. Rahal, A.; Kumar, A.; Singh, V.; Yadav, B.; Tiwari, R.; Chakraborty, S.; Dhama, K. Oxidative stress, prooxidants, and antioxidants: The interplay. *BioMed Res. Int.* **2014**, *2014*, 761264. [CrossRef]
202. Zhang, H.-M.; Zhang, Y. Melatonin: A well-documented antioxidant with conditional pro-oxidant actions. *J. Pineal Res.* **2014**, *57*, 131–146. [CrossRef]
203. Hacışevki, A.; Baba, B. An Overview of Melatonin as an Antioxidant Molecule: A Biochemical Approach. In *Melatonin—Molecular Biology, Clinical and Pharmaceutical Approaches*; IntechOpen: London, UK, 2018.
204. Tan, D.-X.; Manchester, L.C.; Esteban-Zubero, E.; Zhou, Z.; Reiter, R.J. Melatonin as a Potent and Inducible Endogenous Antioxidant: Synthesis and Metabolism. *Molecules* **2015**, *20*, 18886–18906. [CrossRef] [PubMed]
205. Jockers, R.; Delagrange, P.; Dubocovich, M.L.; Markus, R.P.; Renault, N.; Tosini, G.; Cecon, E.; Zlotos, D.P. Update on melatonin receptors: IUPHAR Review 20. *Br. J. Pharmacol.* **2016**, *173*, 2702–2725. [CrossRef]
206. Sharafati-Chaleshtori, R.; Shirzad, H.; Rafieian-Kopaei, M.; Soltani, A. Melatonin and human mitochondrial diseases. *J. Res. Med. Sci.* **2017**, *22*, 2. [CrossRef]
207. Reiter, R.J.; Rosales-Corral, S.; Tan, D.X.; Jou, M.J.; Galano, A.; Xu, B. Melatonin as a mitochondria-targeted antioxidant: One of evolution's best ideas. *Cell. Mol. Life Sci.* **2017**, *74*, 3863–3881. [CrossRef]
208. Mayo, J.C.; Sainz, R.M.; González-Menéndez, P.; Hevia, D.; Cernuda-Cernuda, R. Melatonin transport into mitochondria. *Cell. Mol. Life Sci.* **2017**, *74*, 3927–3940. [CrossRef]
209. Shneider, A.; Kudriavtsev, A.; Vakhrusheva, A. Can melatonin reduce the severity of COVID-19 pandemic? *Int. Rev. Immunol.* **2020**, *39*, 153–162. [CrossRef]
210. Bahrampour Juybari, K.; Pourhanifeh, M.H.; Hosseinzadeh, A.; Hemati, K.; Mehrzadi, S. Melatonin potentials against viral infections including COVID-19: Current evidence and new findings. *Virus Res.* **2020**, *287*, 198108. [CrossRef]
211. Jørgensen, J.T.; Hersom, M. Companion diagnostics-a tool to improve pharmacotherapy. *Ann. Transl. Med.* **2016**, *4*, 482. [CrossRef]
212. Jørgensen, J.T. Companion diagnostics: The key to personalized medicine. Foreword. *Expert Rev. Mol. Diagn.* **2015**, *15*, 153–156. [CrossRef]
213. Burlea-Schiopoiu, A.; Ferhati, K. The Managerial Implications of the Key Performance Indicators in Healthcare Sector: A Cluster Analysis. *Healthcare* **2020**, *9*, 19. [CrossRef] [PubMed]