Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Immunopharmacology 104 (2022) 108516

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Neutrophil Extracellular Traps (NETs) and Covid-19: A new frontiers for therapeutic modality

Hayder M. Al-Kuraishy [a], Ali I. Al-Gareeb [a], Hany Akeel Al-hussaniy [b], Nasser A. Hadi Al-Harcan [c], Athanasios Alexiou [d,e,*], Gaber El-Saber Batiha [f,*]

[a] Department of Clinical Pharmacology and Medicine, College of Medicine, Al-Mustansiriyiah University, Baghdad, Iraq
[b] Department of Pharmacology, College of Anesthetic, Al-Nukhaba University-Baghdad, Iraq
[c] Department of Clinical Pharmacology and Medicine, College of Medicine, Al-Rasheed University College, Bagdad, Iraq
[d] Department of Science and Engineering, Novel Global Community Educational Foundation, Hebersham, Australia
[e] AFNP Med Austria, Wien, Austria
[f] Department of Pharmacology and Therapeutics, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, Al Beheira, Egypt

ARTICLE INFO

Keywords:
Covid-19
Neutrophil extracellular traps
Cytokine storm
Immuno-thrombosis
Acute lung injury
Acute respiratory distress syndrome

ABSTRACT

Coronavirus disease 2019 (Covid-19) is a worldwide infectious disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2). In severe SARS-CoV-2 infection, there is severe inflammatory reactions due to neutrophil recruitments and infiltration in the different organs with the formation of neutrophil extracellular traps (NETs), which involved various complications of SARS-CoV-2 infection. Therefore, the objective of the present review was to explore the potential role of NETs in the pathogenesis of SARS-CoV-2 infection and to identify the targeting drugs against NETs in Covid-19 patients. Different enzyme types are involved in the formation of NETs, such as neutrophil elastase (NE), which degrades nuclear protein and release histones, peptidyl arginine deiminase type 4 (PADA4), which releases chromosomal DNA and gasdermin D, which creates pores in the NTs cell membrane that facilitating expulsion of NT contents. Despite of the beneficial effects of NETs in controlling of invading pathogens, sustained formations of NETs during respiratory viral infections are associated with collateral tissue injury. Excessive development of NETs in SARS-CoV-2 infection is linked with the development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) due to creation of the NETs-IL-1β loop. Also, aberrant NTs activation alone or through NETs formation may augment SARS-CoV-2-induced cytokine storm (CS) and macrophage activation syndrome (MAS) in patients with severe Covid-19. Furthermore, NETs formation in SARS-CoV-2 infection is associated with immuno-thrombosis and the development of ALI/ARDS. Therefore, anti-NETs therapy of natural or synthetic sources may mitigate SARS-CoV-2 infection-induced exaggerated immune response, hyperinflammation, immuno-thrombosis, and other complications.

1. Introduction

Covid-19 is a global pandemic infectious disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), affecting various organ types, principally the respiratory system, and presenting with pulmonary and extra-pulmonary manifestations [1]. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are the most severe pulmonary manifestations. However, extra-pulmonary manifestation likes acute cardiac injury, neurological disorders, pancreatic injury, and acute kidney injury (AKI) are evident [1]. This systemic effect of Covid-19 is linked with the wide distribution of angiotensin-converting enzyme 2 (ACE2), which is an entry point for SARS-CoV-2 [2]. It has been shown that ACE2 is highly expressed in various tissues, including lung alveolar cells type II, proximal renal tubules, immune cells, and intestines [3]. Furthermore, the binding of SARS-CoV-2 to the ACE2 is linked with down-regulation of ACE2, intensification in the level of harmful angiotensin II (AngII), reduction of protective Ang1-7, Ang1-9, and release of pro-inflammatory cytokines [4].

The World Health Organization (WHO) declaration that this disease is a pandemic, and till late March 2021, the total established cases are 123,012,799, with 2,715,472 deaths. In this universal dilemma, diverse efforts and advancing research are built-up to find effective agents

Abbreviations: ALI, ARDS.

* Corresponding authors at: Department of Science and Engineering, Novel Global Community Educational Foundation, Hebersham, Australia (A. Alexiou).
E-mail addresses: alexiou@ngcef.net (A. Alexiou), dr_gaber_batiha@vetmed.dmu.edu.eg (G.E.-S. Batiha).

https://doi.org/10.1016/j.intimp.2021.108516
Received 2 December 2021; Received in revised form 30 December 2021; Accepted 31 December 2021
Available online 6 January 2022

against SARS-CoV-2 from recent or old approved drugs as a repurposing drug strategy [5]. Older age groups and comorbidities such as hypertension, diabetes mellitus, and chronic kidney disease are linked with Covid-19 severity [6]. Regarding the clinical presentations of Covid-19 patients, most of them are asymptomatic or have mild symptoms; however, 10%-20% of them developed and experienced severe to critical clinical presentations with progression of ALI due to the development of hypercytokinemia and cytokine storm (CS) [7].

Generally, in severe SARS-CoV-2 infection, there are strong inflammatory reactions because of neutrophil recruitments and infiltration in the different organs with the formation of neutrophil extracellular traps (NETs), which involved with various severe consequences of SARS-CoV-2 infection such as ALI, ARDS, CS, pulmonary thrombosis and multi-organ damage (MOD) [8].

Thus, the present study aimed to explore the possible role of NETs in the SARS-CoV-2 infection and to identify the targeting drugs against NETs in Covid-19.

2. Neutrophil extracellular traps and respiratory viral infections

Neutrophils (NTs) represent approximately 60% of blood leukocytes and are the primary immune cells and first-line guard alongside entering pathogens [206]. Typically, NTs are formed in humans each day; they have a short half-life and high metabolic functions [9]. It has been reported that NTs are often also participating against viral infections; thereby, a large number of NTs are accumulated in the pulmonary circulation in a steady state due to frequent interactions with invading respiratory viruses [10]. However, exaggerated immune function and activity of NTs are associated with the development of ALI due to the generation of free radicals, reactive oxygen species, and discharge of harmful proteolytic enzymes [11].

In respiratory viral infections, NTs and other phagocytic cells leave circulation and resident infected pulmonary sites in response to the inflammatory cytokines, chemokines, interferon (IFN), and pathogen-associated molecular patterns (PAMPs) [12]. Likewise, NTs are contemporary in the respiratory tract and show an important role in respiratory immunity against influenza A and avian influenza viruses. In addition, higher NTs in the lower respiratory tract during acute influenza A infection are linked with the infection severity [13].

Furthermore, NTs illustrate a more vigorous and dynamic defense against respiratory viral infection and other type of infections in cooperation with platelets in forming NETs that protect from viral infections [14] [Fig. 1].

Besides, NETosis is defined as the formation of NETs during NTs programmed cell death [14]. In addition, the formation of NETs may also develop without damage to the NT cell membrane with preserving normal phagocytic and chemotactic functions [15,207]. Both NETs and NETosis control viral severity; Hiroki et al [16] illustrated that NETosis is a natural process that prevents acute Chikungunya viral infection by reducing systemic viral load.

NETs are net-like structures consisting of neutrophil granule proteins, DNA, and chromatins expelled from the NTs to ensnare invading pathogen [208]. Different enzyme types are involved in the formation of NETs, such as neutrophil elastase (NE), which degrades nuclear protein and release histones, peptidyl arginine deiminase type 4 (PADA4) that releases chromosomal DNA and gasdermin D that creates damage in the NTs cell membrane that facilitating expulsion of NT contents [17]. Despite the beneficial effects of NETs in controlling invading pathogens, sustained formations of NETs during respiratory viral infections are associated with a collateral tissue injury [18]. In addition, various studies showed that higher and excessive formations of NETs might activate inflammatory reactions that induce systemic coagulopathy, localized micro-thrombosis, and MOD [17] (Fig. 2).

The interaction between the viruses and the NTs in the induction of NETs and NETosis is ill-defined; however, it may be direct or indirect interactions [19]. Different types of viruses at a low level can stimulate NTs in vitro to produce NETs [19]. The virus can enter the NT and induce NETs or NETosis through specific surface or endosomal pattern recognition receptors (PRRs) of NTs; for example, the NTs sense human immune deficiency virus (HIV) via Toll-like receptors (TLR) type 7 and 8, and consequently undergo NETosis [20]. Also, through its fusion protein, respiratory syncytial virus (RSV) can interact with the NT TLR4 for induction of NETs and with β2-integrins for induction of NETosis [21]. On the other hand, the viruses can induce NET formations via the PRRs-independent pathway; the inflammatory chemokines and cytokines such as INF and IL-8 are engaged with NET generation [22,209]. Also, activated platelets during viral infections may play a role in inducing NET formations [23].

In this regard, some NTs are susceptible and primed for NET formations, either NETs or NETosis; however, most NTs are switched for phagocytic action rather than apoptotic pathway depending on the antiviral effector program of the NTs [24]. Thus, some proportion of the NTs is subjected to NETosis while other proportion forms NETs. The structure and function of NETs induced during viral infections are substantially different from that induced by bacterial infections and metabolic diseases [24,210,211].

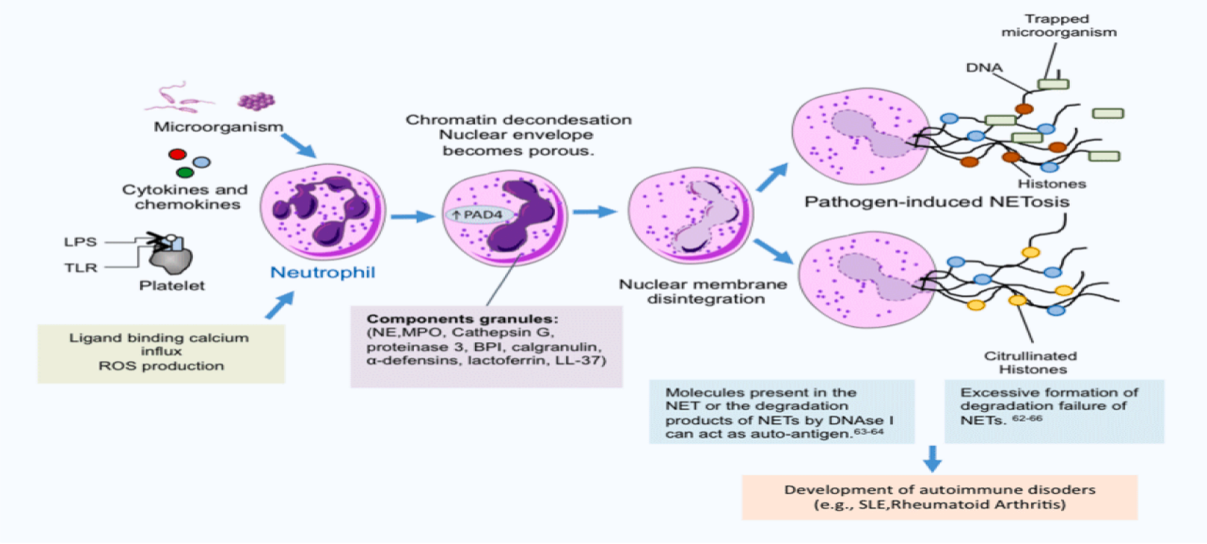

Fig. 1. Neutrophil extracellular traps in infections.

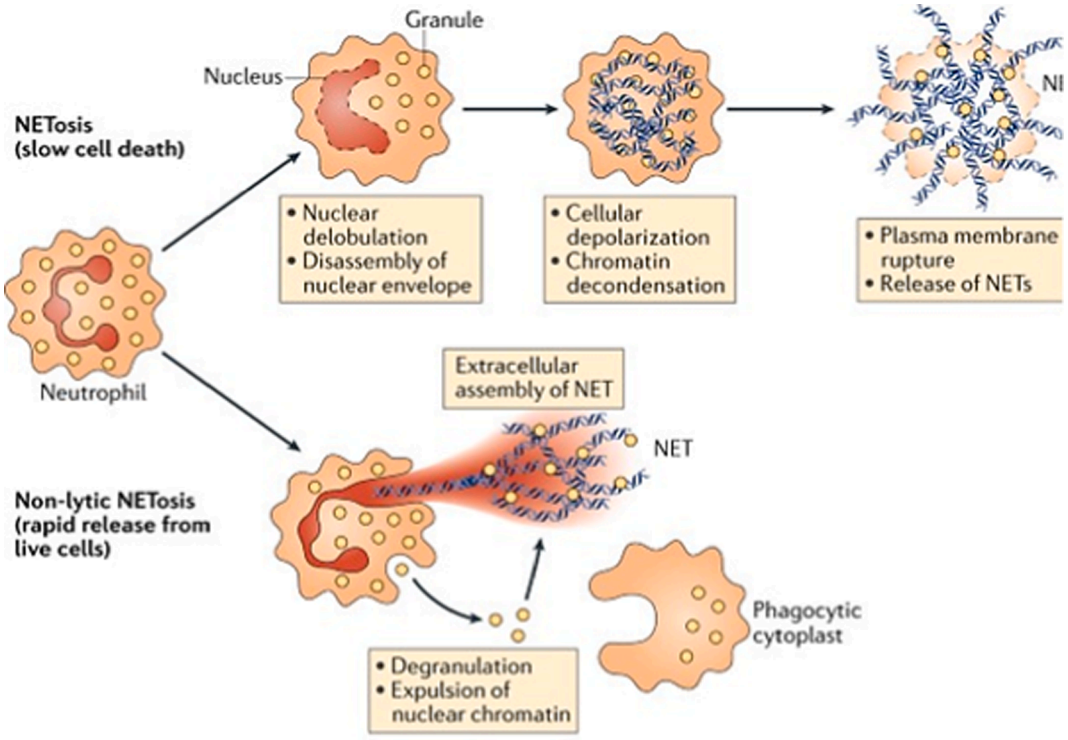

Fig. 2. Generation of Neutrophil extracellular traps (adopted from Papayannopoulos 2018 [17].

NETs formation during acute viral infections might be valuable in restricting viral spread; chromatins of NETs bind and restrain viral particles through electrostatic attractions since the histones are positive charge molecules that can bind the negative charge viral envelopes proteins [25]. Also, NETs histones can induce aggregation of influenza particles, inhibit HIV transcription, prevent adsorption of noroviruses [25].

Further, NETs also contain different antiviral molecules such as cathelicidins and myeloperoxidase, which inactivate a wide range of enveloped and non-enveloped viruses [26]. In addition, NETs components may improve antiviral immunity. For example, Xu et al. [27] exhibited that high mobility group box-1 proteins and histones may trigger the release of pro-inflammatory cytokines and chemokines from other immune cells; however, this process is limited since high NETs

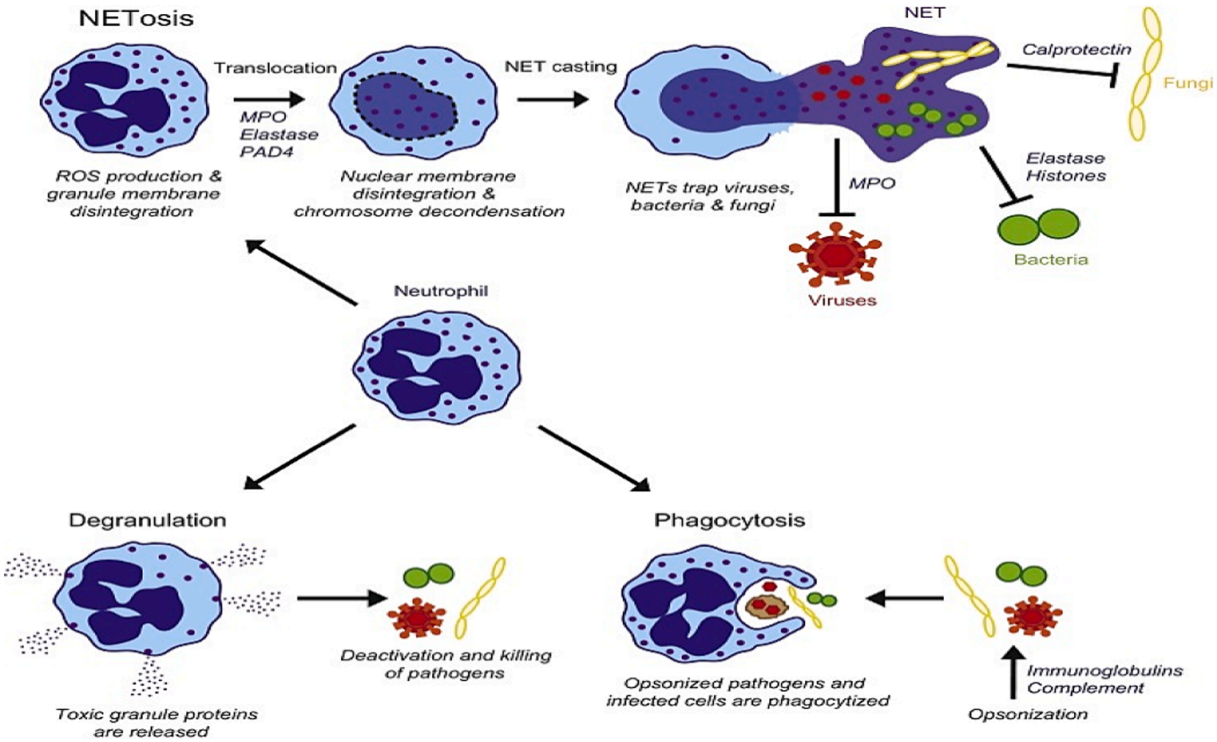

Fig. 3. Neutrophil extracellular traps and invading pathogens (adopted from Cortjens et al., 2017 [28]).

aggregates, degrade and metabolize these chemokines and cytokines [28]. Alongside, NETs also can trigger innate immunity through activation release of IFN from dendritic cells and adaptive immunity via activation of T lymphocytes [28] (Fig. 3).

Into the bargain, the virus can evade the NETs through induction the release of IL-10 from dendritic cells, which inhibit NTs TLR-mediated activation. For example, the Dengue virus inhibits NETs formation via reduction of glucose uptake, and the Herpes virus has DNAase activity, which degrades the formed NETs [29].

These observations demonstrated the potential role of NETs formation in limiting of various viral infections.

3. Covid-19 and neutrophil extracellular traps

In patients with Covid-19, the NTs number is increased with significant lymphopenia, so neutrophil-lymphocyte ratio (NLR) is augmented [212]. High NLR is correlated with underlying inflammatory reactions and is an independent risk factor for Covid-19 severity [30]. In SARS-CoV-2 infection, different chemokines and cytokines that act as NTs attractants are elevated primarily in patients with severe Covid-19, suggesting the possible role of the NTs against SARS-CoV-2 [31]. It has been reported that the lungs autopsies of patients with Covid-19 have high NTs infiltrations characterized by neutrophilic mucositis, acute capillaritis, and fibrin deposition with neutrophilic extravasations into the air space [8]. High NTs in the pulmonary microcirculation and the activated platelets are entrapped with subsequent degeneration and formation of NETs [8]. The expelled contents from deranged NTs such as free DNA, citrullinated histones, and myeloperoxidase (MPO) are deposited within NETs; some of these contents are released into the circulation, and their levels are correlated with NETs density and Covid-19 severity [32]. SARS-CoV-2, like other viruses, can directly trigger the formation of NETs by unidentified mechanism; however, indirect activation of NETs formation in Covid-19 might be due to SARS-CoV-2–induced CS and down-regulation of ACE2, which inhibits NTs infiltrations [33]. Indeed, formed ROS during SARS-CoV-2 infection directly activates both NETs formation inflammatory cascades in a vicious cycle [34] (Fig. 4).

4. Nets and acute lung injury in Covid-19

The NETs are highly toxic to the vascular endothelium and lung epithelial cells due to their contents, which are histones, MPO, defensins, and cathelicidins [18]. For example, histone has the robust cationic property that binds negative charge host cell membrane leading to cell lysis, tissue damage, and induction of inflammations [18]. Therefore, anti-histone antibody and neutrophil esterase blocking antibodies may reduce NETs-induced tissue damage and ALI [35]. Thereby, SARS-CoV-2-induced ALI and ARDS might be mediated by induction of NETs formation [213]. Yaqinuddin et al. [36] reported that excessive NETs development is related to the progression of ALI and ARDS due to the creation of the NETs-IL-1β loop that is exaggerated and can cause inflammatory-induced lung damage. NETs-IL-1β loop is developed due to activation of IL-1β by the NETs, and also IL-1β stimulates NETs formation [36]. As well, NETs-IL-1β loop is also created due to activation nod-like receptor pyrin 3 (NLRP3) inflammasome of lung macrophages by NETs during acute SARS-CoV-2 infection the macrophages extrude their contents to form macrophage extracellular traps (METs) similar to that of NETs [213]. NETs drive only pro-inflammatory macrophages (M1) to form METs in response to netting pulmonary NTs [37]. Formations of both NETs and METs in the lung are associated with localized lung pathology in a marginated pool manner; however, in severe cases, this reaction may spill over and extend to the systemic circulation leading to more severe inflammatory reactions and development of complications [38]. From a clinical point of view, old age is a sovereign risk factor for the development of ALI and ARDS in SARS-CoV-2 infection [39], though NETs formation is reduced in the elderly [40]. The possible explanation of this phenomenon is that NETs formation is beneficial in the early stage to eliminate the invading virus; thus, SARS-CoV-2 infection may be exacerbated in a steady-state in the old-age group, causing more ALI ARDS and other complications [41].

On the other hand, platelets of elderly patients are unstable and prone to overactivation in triggering NTs for NETs formation [42]. Moreover, overstated management of ALI or ARDS by high-pressure oxygen therapy may increase the risk of more ALI through induction of NETs formation [43]. Alongside, lipid-lowering statins commonly

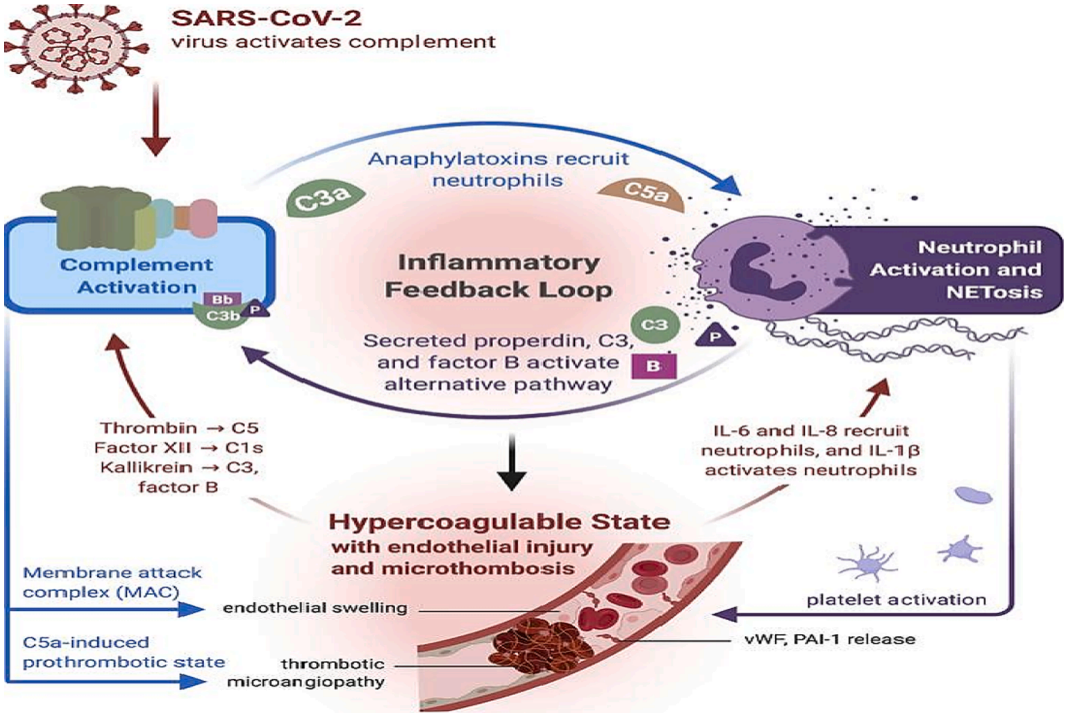

Fig. 4. Neutrophil extracellular traps and Covid-19 (Adopted from Java et al., [34]).

prescribed in the elderly Covid-19 patients are associated with enhancing NETs formation [44].

NETs formation has been linked to the development of different respiratory disorders including; asthma, cystic fibrosis, acute bacterial pneumonia, and chronic obstructive pulmonary disease (COPD) [45]. Experimental animal studies have shown the pathologic role of NETs in the induction of ALI, and loss of NETs contents and neutrophil granules may reduce the risk for the development of ALI in mice [18]. A recent mouse model revealed that released histone-DNA complexes of NETs activate macrophages and other immune cells through activation of TLR9 with subsequent stimulation the release of TNF-α and IL-6 [46]. Therefore, NETs formation during SARS-CoV-2 infection may cause ALI and ARDS directly or indirectly through activation of TNF-α, IL-6, and IL-1β with induction of CS [47]. During the development of CS, the pro-inflammatory cytokines lead to uncontrolled interactions between the NTs and macrophages with subsequent progressive inflammation [48]. IL-6 binds IL-6Rα to be intimate with the pro-inflammatory state; in this way, the NTs can shed IL-6Rα that augment the pro-inflammatory effect of IL-6 in the induction of CS-induced ALI [8].

In this context, aberrant NTs-induced CS in Covid-19 vastly differs from INF-induced CS in macrophage activation syndrome (MAS) [49]. However, uncontrolled NTs activation by PAMPs from SARS-CoV-2 injured cells may lead to robust activation of macrophages with a considerable amount of pro-inflammatory cytokines, which is linked with the development of ALI and ARDS [50]. Hu et al. [51] observed that NETs formation contributes to activation of MAS through activation of NLRP3 inflammasome in adult-onset Still disease.

Therefore, these findings revealed that aberrant NTs activation alone or through NETs formation might augment SARS-CoV-2-induced CS and MAS in patients with severe Covid-19. Wang et al.'s [52] retrospective study involving 55 Covid-19 patients illustrated that neutrophilia and NETs formation are correlated with ALI and high lung computed tomography score. Indeed, plasma levels of NETs are correlated with SARS-CoV-2 viral load and associated inflammatory cytokines and chemokines [53].

Thereby, these experimental and clinical studies document that neutrophilia and NETs formation are highly implicated in the pathogenesis of ALI and ARDS in severe Covid-19 (Fig. 5).

5. Nets and coagulopathy in Covid-19

It has been shown that severe SARS-CoV-2 infection is associated with coagulopathy and thrombosis, which might drive for Covid-19 severity [54]. Micro-vascular injury-induced endothelial dysfunction and the formation of anti-phospholipids antibodies could be the initial step in the development of disseminated intra-vascular thrombosis and localized pulmonary micro-thrombosis [55]. Coinciding with this notion, the biomarker of coagulopathy and fibrin degradation such as D-dimer is elevated and correlated with mortality in patients with severe Covid-19 [56]. Different studies proposed that NETs formation in Covid-19 might be the potential cause of venous and arterial thrombo-embolism due to vasculitis and immune-mediated mechanism [57]. A recent experimental study by Hisada et al. [58] confirmed that high plasma NETs level is associated with developing venous thrombosis in mice. However, the precise mechanism of NETs-induced thrombosis is ill-defined.

Nevertheless, diverse studies revealed that platelet activation and immune-mediated fibrin formation could be the proposed mechanisms [59]. During inflammatory reactions caused by dissimilar metabolic and infectious disorders, the platelets membrane-bound TLR4 are activated and interact with the NTs in the formation of NETs [59]. In this way, the NETs also activate the platelet via P-selectin, leading to platelet aggregation and thrombosis [60]. Notably, during mild SARS-CoV-2 infection, physiological immuno-thrombosis is developed and controlled by body homeostatic mechanism; however, in severe SARS-CoV-2 infections, uncontrolled physiological immuno-thrombosis may be controlled extend and develop into pathological immuno-thrombosis [61]. Besides, pathological immuno-thrombosis highly targets pulmonary and renal micro-circulations, leading to ALI [62] and acute kidney injury [63] in censoriously ill Covid-19 patients. Additionally, NETs formation in Covid-19 may induce- Kawasaki-like vasculitis and coagulopathy in infants and children with mild SARS-CoV-2 infections [64].

On the other hand, Skendros et al.'s [65] case-controlled study illustrated that activation of both NTs and complemented contribute to inducing thrombotic microangiopathy and hyperinflammation in patients with Covid-19. Complement activation drove immune cells, mainly monocytes, and NTs, to the site of lung injury, and in concert with platelets, can induce micro pulmonary thrombosis and systemic immuno-thrombosis [34]. Various studies showed that sera of Covid-19 patients contain a lot of immune complexes and autoantibodies that activate the complement cascade, mainly C3 [66]. Also, SARS-CoV-2 virions such as nucleocapsid protein can activate C3 through lectin dependent pathway [66]. Complement activations trigger tissue factor expression on the NT cell membrane with significant platelet activation leading to NETs formation and immuno-thrombosis [67]. Therefore, C3 inhibitor (AMY-101) inhibits immuno-thrombosis and thrombo-

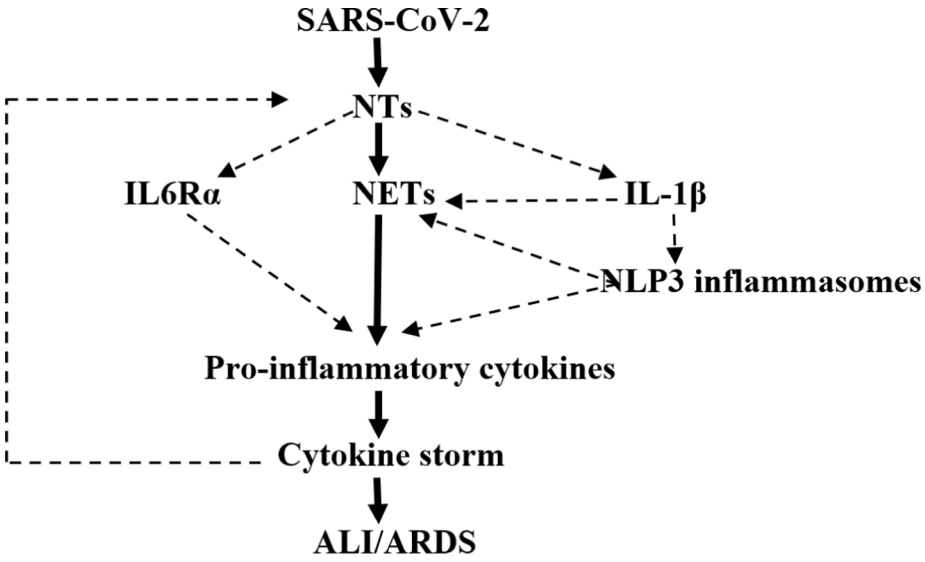

Fig. 5. Neutrophil extracellular traps and acute lung injury in Covid-19.

inflammatory response to the SARS-CoV-2-induced microvascular injury [68].

Similarly, compstatin (C3 inhibitor) inhibits C3-induced formation of NTs-platelet complex and NETs production with subsequent suppression of micro-vascular thrombosis [69]. Therefore, C3 inhibitors may reduce NETs-induced immuno-thrombosis and the development of ALI and ARDS in patients with Covid-19 [70]. Indeed, NETs contents can directly lead to immuno-thrombosis and thrombo-inflammatory [70]. Middleton et al. [71] illustrated that the high MPO-DNA complex released from NETs in the plasma of Covid-19 patients is linked with pulmonary micro-thrombosis and ARDS. In addition, the interaction between NETs and platelet phospholipids activates the plasma kallikrein-kinin system leading to platelet aggregation and thrombosis [72]. Similarly, NETs histones activate platelets TLR causing platelet aggregations [73]. Alongside, progressive binding of NTs to the formed NETs contributes to digestion and degradation of tissue factor inhibitor and anti-thrombin III (natural anticoagulant), thereby augmenting the pro-coagulant activity of thrombin in the induction of intravascular thrombosis [74].

Moreover, NETs deliver extracellular oxidant contents such as nitric oxide synthase, NADPH oxidase, and MPO that serve as a potential source of toxic histones and DNA, which activate the extrinsic coagulation pathway [75]. In contrast, the tissue factor of NETs activates the intrinsic coagulation pathway [75,76]. In addition, neutrophil elastase is present in the NETs inactive tissue factor inhibitor leading to reduction of endogenous anticoagulant activity and augmentation of pro-coagulant activity [74]. Besides, exaggerated innate immune response-induced cytokine release in SARS-CoV-2 infection may lead to endothelial dysfunction and activation of the pro-coagulant cascade [77]. Furthermore, Zuo et al. [57] showed a positive correlation between NETs blood level and D-dimer, suggesting a potential link between NETs formation fibrin degradation products, and activated prothrombotic pathway.

Thus, a new perspective about the critical role of NETs in the induction and initiation of thrombosis and coagulopathy suggested that NETs act as a scaffold for thrombus formation through promoting erythrocyte and platelet adhesions by concentrating coagulation factors and effectors proteins [78]. Therefore, these findings highlighted the intricate relationship between endothelial dysfunction and platelet activation during NETs formation-induced thrombosis in patients with SARS-CoV-2 infection (Fig. 6).

6. Nets and comorbidities in Covid-19

Diabetes mellitus (DM), hypertension (HT), obesity, and other cardio-metabolic disorders are the commonest comorbidities risk factors that increase Covid-19 severity [79]. However, DM is regarded as one of the most distinctive risk factors for Covid-19 and 16.2% of patients with severe Covid-19 had DM, which might explain the high case fatality in diabetic Covid-19 patients [80]. This may be due to exaggerated pro-inflammatory response and dysfunction of innate immunity [80]. Hyperglycemia in DM primes NTs to release and form NETs; hyperglycemia also induces the NTs to produce Ca-binding protein S100 A8/A9 (S100A8/A9) that activates the release of hepatic thrombopoietin and subsequent thrombosis [81]. In addition, Th17-associated cytokines are increased in both DM and Covid-19 that trigger an exaggerated immune response and NETs formation [50]. Of note, exaggerated NETs formation due to underlying metabolic and inflammatory reactions in DM may lead to abnormal immune response and cytokine deregulation in SARS-CoV-2 infection [82].

Moreover, hyperglycemia and associated ROS lead to the pre-activation of NTs for the production and release of NETs when activated by various stimuli [83]. NTs from diabetic patients also produce more IL-6 and are more susceptible to NETs formation [83]. Hyperglycemia-induced NETs formation is performed through activation of NADPH oxidase in a concentration-dependent manner; therefore, NADPH oxidase inhibitors reduce NETs formation in DM [84]. Thus, NETs formation in diabetic patients with Covid-19 is exaggerated due to the dual effect of hyperglycemia and SARS-CoV-2 in activating NADPH oxidase [85]. Therefore, the net-final effect of DM in the augmentation of Covid-19 severity is might be the NETs formation.

On the other hand, cardiovascular diseases such as HT, endothelial dysfunction, coronary heart disease (CHD), acute cardiac injury (ACI) are common in comorbidities linked with Covid-19 severity [86]. These complications are developed due to direct SARS-CoV-2 injury or indirectly through ACE2 down-regulation and development of CS [86]. Exaggerated AngII level with reduction of vasodilator Ang1-7 due to SARS-CoV-2 -induced down-regulation of ACE2 might be the proposed mechanisms of cardiovascular injury in Covid-19 [87]. Alongside, down-regulation of ACE2 may increase NTs infiltration and NETs formation with subsequent endothelial injury-mediated thrombosis and pulmonary hypertension [88]. Li et al. [89] showed that patients with essential hypertension have a hypercoagulability status due to higher NETs formation. Indeed, NETs formation may exacerbate endothelial injury and coagulation in hypertensive patients [90]. Therefore, NETs formation might be the potential link between Covid-19 and HT [Fig. 7].

Similarly, NETs are intricated in the pathogenesis of acute myocardial injury (AMI) since NETs increase fibrin formation and deposition at the site of plaque rupture in the coronary vessels [91]. In this site, NETs

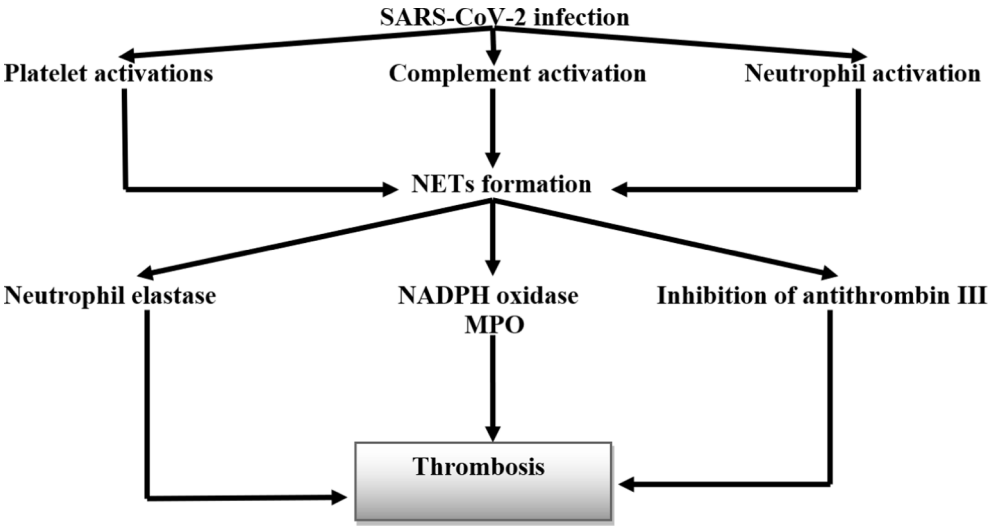

Fig. 6. Neutrophil extracellular traps and coagulopathy in Covid-19.

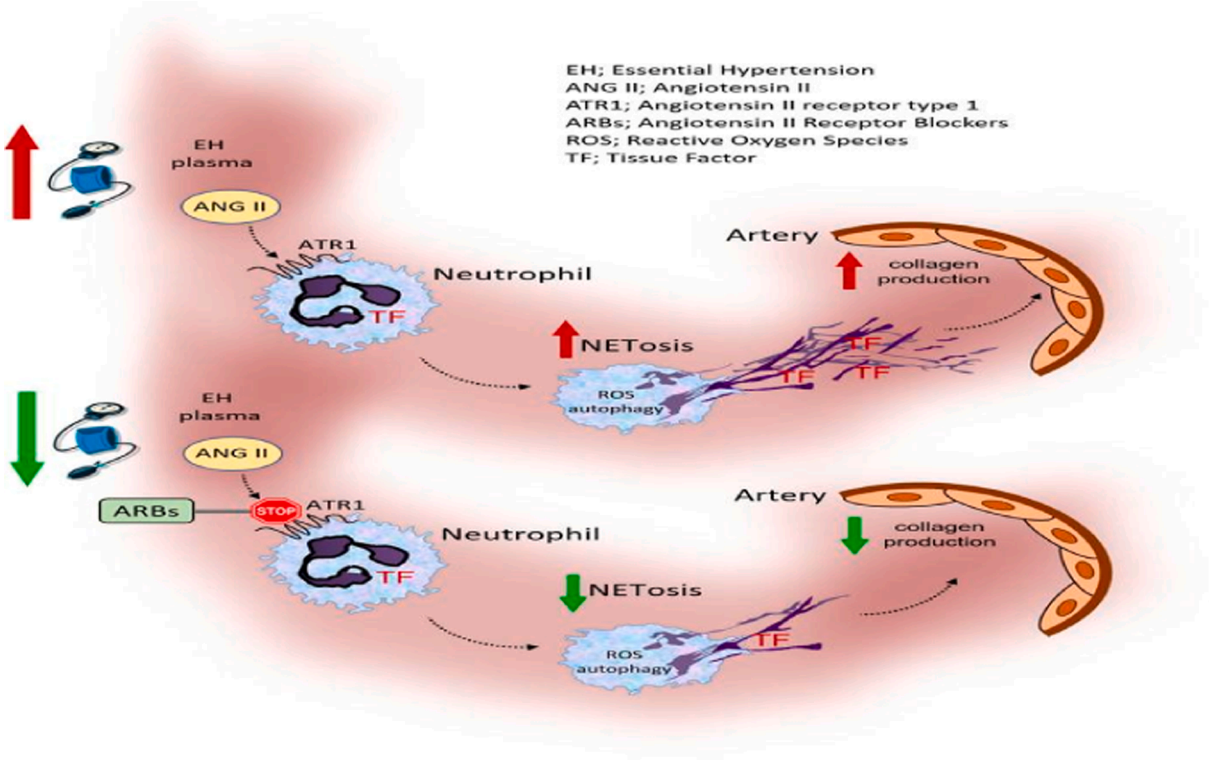

Fig. 7. Neutrophil extracellular traps and hypertension.

release functional tissue factors, which enhance platelet activation and thrombin generation [92]. In this way, the activated platelets promote NETs formation at the site of AMI [92]. Wei et al. 's [93] prospective study involved 101 Covid-19 found that 15.8% of them presented with AMI and they needed mechanical ventilation, all of the patients had a poor prognosis. The fundamental mechanisms of AMI in Covid-19 might be due to direct SARS-CoV-2, SARS-CoV-2-induced down-regulation of ACE2, and SARS-CoV-2 -induced CS [94,95]. Kounis et al. [96] reported that AMI in Covid-19 might be due to activation and upregulation of prothrombotic factors such as NETs, von-Willebrand factor, factor VIII, and D-dimer. These observations shed light on the critical role of NETs as they link the pathogenesis of AMI and ARDS in Covid-19.

Furthermore, obesity, which is considered an inflammatory status due to adipose tissue dysfunction, is commonly associated with cardiovascular complications that increase the risk for Covid-19 [97,98]. NETs are increased in obesity due to augmentation of immune cell infiltrations into adipose tissue with subsequent chronic adipose tissue-mediated inflammatory reactions [99]. Therefore, NETs inhibitors may attenuate obesity-induced endothelial dysfunctions and coagulation disorders [100]. Surprisingly, platelet activations are reduced during sepsis in obesity with reducing of NETs formation [101]. Furthermore, experimental studies illustrated that a high-fat diet increases the expression of cathelicidin, a specific marker of NETs formation in mice [102]. Therefore, obesity-mediated NETs formation and endothelial injury might raise the risk of coagulopathy in SARS-CoV-2 infection [103]. Since MPO-DNA complexes linked with immunothrombosis are elevated in obese patients and do not return to the baseline level even after gastrectomy, since reduction in the body weight and body mass index did not affect immunological reactivity of NTs and propensity for NETs formation [104]. Taken together, cardio-metabolic comorbidities may increase Covid-19 severity mainly through potentiating of NETs formation that amplifies the risk of coagulopathy, ALI, and ARDS [105].

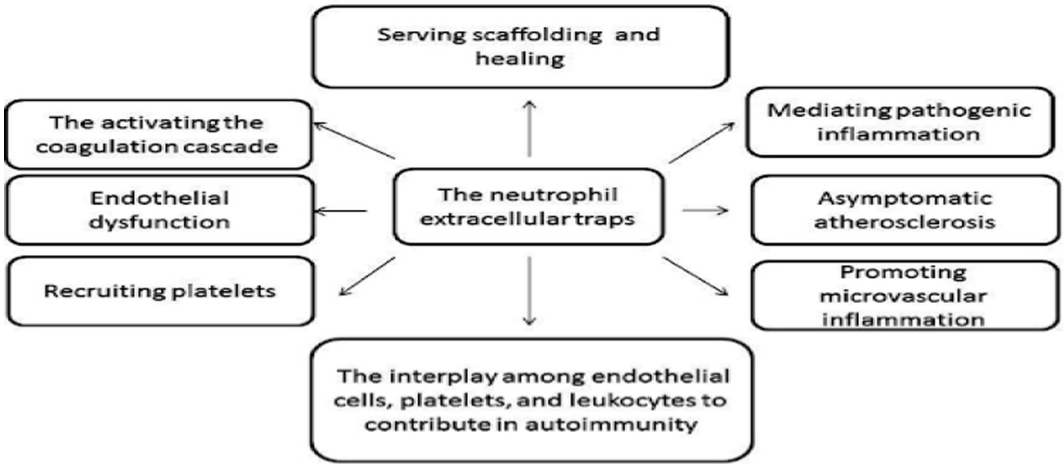

Fig. 8. Different effects of activated neutrophil extracellular traps in Covid-19.

Taken together, NETs formation lead to diverse effects in SARS-CoV-2 infection that can cause different complications [Fig. 8].

7. Nets inhibitors as a therapeutic modality for Covid-19

7.1. Endogenous NETs inhibitors

Endogenous NETs inhibitors such as neonatal NET-inhibitory factor (nNIF) inhibit the critical factors in NETs formation such as histone citrullination, nuclear condensation, and activity of peptidyl arginine deiminase 4(PADA 4) [106]. Also, nNIF inhibits pathogens, and microbial toxins-mediated NETs formation, thereby reducing systemic inflammation-induced collateral tissue damage [106]. Campbella et al.'s [107] study illustrated that nNIF is highly circulated in fetal circulation and generated by the action of placental alpha-1-antitrypsin. This nNIF is responsible for immunological tolerance during the transition from intrauterine to extrauterine life, so NTs isolated from the umbilical cord of preterm neonates are defective for NETs formation and bacterial killing [108]. Furthermore, it has been shown that nNIF may attenuate respiratory syncytial virus infection-induced NETs formation in the preterm neonate [109]. Pertiwi [110] suggests that nNIF might be a promising agent targeting NETs in managing Covid-19 severity.

Prostaglandins (PGs) are eicosanoids synthesized in the body by the action of cyclooxygenase (COX) enzyme from arachidonic acid (AA) [111]. PGE2 is the most abundant one has both inflammatory and anti-inflammatory actions [112]. It has been reported that PGE2 inhibits NETosis and NETs formation through activation of protein kinase A and cAMP that are potent inhibitors of NETs formation [113]. It has been shown that over-expression of COX2 in the NTs is associated with the defective killing of intracellular pathogens due to reduction in NETs formation [114]. Therefore, the PGE2 antagonist restores NETs formation [114].

Moreover, a peptide inhibitor (PA-Dpeg24) of complement C1-dependent MPO activation inhibits inflammatory reactions and NETs formation in the transplanted tissues [115]. Therefore, PGE2 inhibits NETs formation through attenuation of complement activation. However, PGE2 serum level is increased in Covid-19, and COX-2 inhibitors might be beneficial in the restoration of human immune response [116]. Inhibition of COX-2 is associated with the elevation of AA, an endogenous antiviral substance associated with inhibiting enveloped viruses such as SARS-CoV-2 and human immune deficiency (HIV) [117]. Therefore, there is a controversy about the potential role in the management of SARS-CoV-2-induced NETs formation.

Thrombomodulin is a cofactor protein mainly expressed on the vascular endothelial cells, modulates thrombin activity [118]. Thrombomodulin-thrombin complex stimulates protein kinase C, which is essential for the anticoagulant pathway [118]. It decreased in sepsis and severe viral infection due to its downregulation by inflammatory cytokines [119]. NETs block fibrinolysis and activate aggregation of platelets, erythrocytes, fibrin, and other clotting factors in the induction of immuno-thrombosis [120]. Recombinant human thrombomodulin (rhTM) inhibits NETosis and NETs formation [120]. Shrestha et al. [121] showed that rhTM inhibits histone-induced NETs release in vitro and in vivo. Also, rhTM attenuates NETs-induced ALI by reducing NETs accumulation and toxic effects of histone [122]. In Covid-19, SARS-CoV-2 infection is related to high inflammatory cytokine angiopoietin-2 (ANGPT2), which inhibits thrombomodulin-thrombin complex with reduction of physiological anticoagulant [123]. It has been hypothesized by Mazzeffi et al. [124] that administration of rhTM in critically Covid-19 patients may reduce ALI/ARDS via inhibition of NETs formation-induced coagulopathy.

Activated protein C (APC), a serine protease enzyme, has anti-inflammatory, cytoprotective, and anticoagulant effects [125]. APC inhibits the release of extracellular histone, activation of clotting factors, and NETs accumulation and formation [125]. Different preclinical studies demonstrated that APC inhibits thrombin generation and excessive inflammation and ischemic-reperfusion-induced tissue injury in bacterial pneumonia [126]. APC also has a protective effect against the development of SARS-CoV-2-induced endothelial injury and coagulopathy via suppression of NETs formation [127]. Guglielmetti et al. [128] offered that recombinant APC might be a therapeutic strategy in Covid-19 through inhibiting inflammation and associated coagulopathy. In critically Covid-19 patients, severe inflammation and thrombosis are the primary determinant factors due to deficiency of APC [129]. In a case series of 10 Covid-19 patients' activities of APC and anti-thrombin are reduced with significant elevation of factor VIII and fibrinogen plasma levels, suggesting a state of hypercoagulability in critically severe Covid-19 patients [130]. Therefore, APC-based therapy is recommended in severely Covid-19 patients to prevent NETs-induced inflammation and coagulopathy.

Anti-high mobility group box-1 (HMGB1) is an endogenous protein released from platelets. It has pro-inflammatory action and regulates NTs chemotaxis [131]. HMGB1 induces thrombus formation, NETosis, and NETs formation through cGMP-dependent activation of platelet-neutrophil interaction [131] Exposure of NTs to the higher concentration of HMGB1 results in NETs formation in vitro [132]. Therefore, anti-HMGB1 antibodies may inhibit NETs formation with reduction of circulating DNA-histone complexes [133]. Moreover, anti-HMGB1 antibodies inhibit NETs formation and pro-inflammatory induced-ALI [134]. Street [135] observed that HMGB1 activates autophagy which is concerned with SARS-CoV-2 entry and replication [136]. Also, down-regulation of ACE2 by SARS-CoV-2 elicits activation of the HMGB1 pathway with subsequent activation of cytokine storm-induced-ALI/ARDS [136]. Therefore, HMGB1-inhibitors such as hydroxychloroquine, methotrexate, glycyrrhizin, inflachromene, and salicylic acid derivative might reduce Covid-19 severity [136]. Into the bargain, Dinicolantoio et al. [137] showed that melatonin improves the activity of type I immune response through inhibition of the HMGB1 signaling pathway during SARS-CoV-2 infection. Therefore, HMGB1 is regarded as a target for repurposing drugs in the management of Covid-19.

C1 esterase inhibitor (CIE-INH) is an endogenous inhibitor of the C1 protein of the complement system, regulating the kallikrein system and coagulation pathway [138]. CIE-INH is approved for the management of hereditary angioedema and may reduce NETs-mediated ALI [139]. In addition, CIE-INH blocks histone, NETosis, and NETs formation, thereby reducing the risk of ALI/ARDS [140]. Thomson and his colleagues reported that SARS-CoV-2 infection is linked with deficiency of CIE-INH, and rapid improvement in Covid-19 is observed following treatment with CIE-INH [141]. However, an ongoing clinical trial in hospitalized Covid-19 patients is waiting to observe the clinical benefit of conestat alfa (CIE-INH) in treating and preventing SARS-CoV-2 infection [142]. The Brazilian clinical trial started in May 2020 and is expected to be completed in April 2021, using CIE-INH and icatibant (bradykinin inhibitor) to manage Covid-19 [142]. Thus, recombinant CIE-INH might be a possible therapy in the management of patients with severe Covid-19.

Heparin is a natural glycosaminoglycan used as an anticoagulant in managing ischemic heart disease, stroke, and deep vein thrombosis [143]. Heparin attenuates NETosis and NETs formation with reduction of circulating histone and associated NF-κB activation in different inflammatory diseases [144]. Moreover, non-anticoagulant heparin (parnaparin) could be used to manage histone and NETs-induced inflammatory diseases [144]. In addition, heparin has a beneficial effect in managing Covid-19 through endothelial protection and prevention of coagulopathy [145]. However, resistance to the heparin effect may develop in severe Covid-19 due to auto-antibody against activated factor X [146]. Thus, high doses of heparin or switching to low molecular weight heparin are recommended [146]. Nonetheless, heparin therapy has a potential role in managing severe Covid-19 through anti-inflammatory, anti-NETs, improvement of lung oxygenation, and prevention development of ARDS [147].

Human DNAase is a selective enzyme that cleaves and hydrolyzes

human DNA in the sputum and mucous, promoting sputum clearance and reducing bronchial secretions' viscosity [148]. Recombinant human DNAase (rhDNAase) has acute anti-inflammatory effects by suppressing NETosis and NETs formation, reducing NTs infiltrations and expression of thrombin [149]. Wang et al. [150] illustrated that rhDNAase effectively treats severe sepsis by inhibiting ROS and NETs formation. Therefore, rhDNAase effectively reduces the period of mechanical ventilation in critically severe Covid-19 patients [151].

7.2. Exogenous NETs inhibitors

Antibiotics may have immunomodulating effects through suppression of NETosis and NETs formation and release of pro-inflammatory cytokines [152]. Azithromycin and other macrolides and chloramphenicol have significant anti-inflammatory effects through inhibition of NETs formation [153]. Furthermore, it has been illustrated that azithromycin inhibits cytokine production, mucin secretion, and bronchial cell proliferation by inhibiting mitogen-activated protein kinase (MAPK) and downstream of the NF-κB pathway [154]. These immunomodulating effects of azithromycin make it a potential candidate in the management of Covid-19 [155]. Furthermore, doxycycline also blocks NETosis and NETs formation with significant immunomodulating effects; thus, it can be used effectively in Covid-19 [2]. Therefore, the pleiotropic effects of antibiotics, mainly anti-inflammatory and immunomodulatory effects and ani-SARS-CoV-2 effect, can subsidize in controlling severe Covid-19 patients [156].

Aspirin (acetylsalicylic acid) is a non-steroidal anti-inflammatory drug (NSAID, has anti-inflammatory and anti-thrombotic effects used in the treatment of various inflammatory disorders [157]. Aspirin inhibits PGs synthesis and causes irreversible acetylation of platelets COX with suppression of thromboxane A2 leading to a noteworthy antiplatelet effect [158]. Furthermore, different studies showed that aspirin inhibits NETosis and platelet activations and NETs formation [159]. During inflammatory conditions, the platelets are activated through TLR2/TLR4, leading to the expression of P-selectin, which induces NTs for NETs formation. In addition, activated platelets secret HMBG-1 and platelet factor 4 that together induce NTs for NETs formation [160]. Therefore, aspirin and other antiplatelet inhibits NTs-platelets interactions and formation of intravascular NETs during endotoxemia-induced ALI [161]. Aspirin also has a direct inhibitory effect on NETs formation via suppression of NTs NF-κB pathway [162]. Recently, aspirin improved clinical outcomes in critically hospitalized Covid-19 patients on mechanical ventilation through suppression of NF-κB pathway and SARS-CoV-2-induced NETs formation [163]. Taken together, aspirin is an effective drug in the prevention of SARS-CoV-2-induced ALI and MOF through mitigation of inflammatory reactions and NETs formation [164].

Sivelestat (ONO-5046) is a competitive, reversible, and selective inhibitor of neutrophil elastase (NEase), not affecting other cellular proteases' activity [165]. Different experimental and preclinical studies showed that sivelestat is effective against ARDS by regulating lung vascular permeability, pulmonary pressure, pathogen clearance, and neutrophil-mediated lung epithelial injury [166]. Okayama et al.'s [167] clinical study observed that sivelestat improves pulmonary function, shortens the duration of mechanical ventilation, and oxygen saturation in patients with systemic inflammatory syndrome and ARDS. Furthermore, Miyoshi et al. [168] illustrated that sivelestat combined with recombinant human soluble thrombomodulin effectively mitigates disseminated intravascular coagulopathy-induced ARDS in intensive care unit (ICU) patients, it increases survival and ventilator-free period. Therefore, sivelestat might be a promising therapy in managing Covid-19-induced ALI, ARDS, and coagulopathy through inhibition of NEase and NETs formation [169]. In addition, sivelestat might be an effective preventive therapy against Covid-19-induced ARDS when given in lymphocytopenic patients before developing neutrophilia and NETs formation [170]. Also, it prevents activation of SARS-CoV-2 S protein and binding with ACE2 [170].

Chloramidine is an inhibitor of protein arginine deiminase (PAD), which is involved in NETs formation and regulation of immune response [171]. Also, chloramidine reduces NETs formation mediated systemic inflammations in the experimental animals [172]. Recently, it has been shown that PAD inhibitors mitigate inflammatory disorders in multiple myeloma [173]. Therefore, chloramidine and other PAD inhibitors reduce NETs formation in different viral infections [174]. Furthermore, up to date, Du et al. [175] illustrated that PAD inhibitors might prevent ALI via suppression of NETs formation. Therefore, chloramidine and other PAD inhibitors might be of potential therapeutic role in managing Covid-19 through suppression of NETs-induced inflammatory burst and coagulopathy [176].

Cyclosporine A is an immunosuppressant agent used to manage autoimmune diseases and organ transplants [177]. It binds cellular cyclophilin and inhibits activated T cells' calcineurin pathway nuclear factor with subsequent inhibition of NETs formation [178]. However, inhibiting NETosis by cyclosporine A may impair the immune response to invading pathogens [179]. In the Covid-19 era, cyclosporine A effectively mitigates exaggerated immune response and cytokine storm with impairment of viral pathogenesis [177,180].

Diphenyleneiodonium chloride (DPI) is an oral hypoglycemic drug that inhibits gluconeogenesis and oxidative stress by inhibiting NADPH oxidase, xanthine oxidase, nitric oxide synthase, and oxidoreductase [181]. It has been proposed that DPI may inhibit the release of extracellular DNA and block NETs formation [182]. In addition, DPI exerted potential antiviral effects via suppression of Zika virus-induced NETs formation [183]. Therefore, DPI may reduce SARS-CoV-2-mediated NETs formation and link ALI and immunothrombosis [184,185].

Metformin is an insulin-sensitizing agent and is regarded as first-line therapy in managing type 2 diabetes mellitus (T2DM) [79]. It acts through the activation of the AMPK pathway that increases cellular glucose uptake (195). In addition, Metformin inhibits oxidative stress and the release of pro-inflammatory cytokines through the AMPK pathway-dependent suppression of the mTORC1 signaling pathway [186]. In addition, Metformin has immunoregulating effects via inhibition of NETosis and NETs formation [187]. Recently, Metformin reduces SARS-CoV-2 pathogenesis and NETs formation with subsequent reduced risk of ALI/ARDS in Covid-19 [188].

Hydroxychloroquine is an antimalarial agent with immunosuppressive and immunomodulating effects used to treat parasitic infections and autoimmune disorders [189]. It inhibits NTs phagocytosis, macrophage activity, and the release of pro-inflammatory cytokines [190]. Hydroxychloroquine suppressed platelets activation and aggregation induced by inflammatory mediators and thrombin [191] and is regarded as an anti-thrombotic agent in anti-phospholipid syndrome [192]. It has been reported that hydroxychloroquine can interfere with NETosis and NETs formation through clocking TLR9 in mice [193]. Boone et al. [194] observed that hydroxychloroquine attenuates hypercoagulability through inhibition of NETs formation. Therefore, hydroxychloroquine may reduce SARS-CoV-2 induced ALI and cytokine storm by inhibiting inflammatory burst and NETs formation [195]. Thus it can be used effectively in the prevention and treatment of Covid-19 [195]. The up-to-date foundation shows that hydroxychloroquine does not affect clinical outcomes and mortality in patients with Covid-19. Still, it is effective as a potential prophylactic agent in the early stage of SARS-CoV-2 infection [196].

N-acetylcysteine (NAC) is a mucolytic agent that decreases mucous viscosity used in the management of paracetamol poisoning, COPD, and oxidative stress treatment [197]. In addition, NAC inhibits ROS-induced NETosis and NETs formation [198] and thrombosis. Thus it may block immunothrombosis in different inflammatory disorders [199]. Recently, NAC has been effective against SARS-CoV-2 infection via interruption of viral replica and development of cytokine storm [200]. In addition, NAC mitigates SARS-CoV-2-induced oxidative stress and endothelial injury and associated coagulopathy through regeneration of endogenous

glutathione [201].

Vitamin D is a fat-soluble secosteroid involved in regulating Ca + 2 serum level and bone mineralization [202]. Vitamin D reduces COPD, respiratory viral infections, pulmonary tuberculosis, and metabolic disorders [203]. Moreover, Vitamin D has immunomodulating effects; it blocks NETosis and NETs formation and regulates innate immune response with inhibition release of pro-inflammatory cytokines [204]. Thus, Vitamin D supplementation may reduce Covid-19 mortality and severity via suppression of cytokine storm and regulation of innate immunity against SARS-CoV-2 infection [205].

8. Conclusion

NETs formation in SARS-CoV-2 infection is linked with critical complications, including ALI and ARDS, due to the development of hyperinflammation, cytokine storm, and immunothrombosis. Therefore, anti-NETs pharmacotherapy might be a promising goal in the management of patients with severe Covid-19. Additional in vitro and in vivo studies and clinical trials and prospective studies are recommended in this regard.

Funding

There is no funding

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] H.M. Al-Kuraishy, A.I. Al-Gareeb, M. Alblihed, N. Cruz-Martins, G.E. Batiha, COVID-19 and Risk of Acute Ischemic Stroke and Acute Lung Injury in Patients With Type II Diabetes Mellitus: The Anti-inflammatory Role of Metformin, Front. Med. 19 (8) (2021 Feb) 110.
[2] H.M. Al-kuraishy, A.I. Al-Gareeb, N. Qusty, N. Cruz-Martins, G.E. Batiha, Sequential doxycycline and colchicine combination therapy in Covid-19: The salutary effects, Pulm. Pharmacol. Ther. 14 (2021 Mar), 102008.
[3] H.M. Al-Kuraishy, A.I. Al-Gareeb, N. Cruz-Martins, G.E. Batiha, Hyperbilirubinemia in Gilbert syndrome attenuates Covid-19 induced-metabolic disturbances: A case-report study, Front. Cardiovascular Med. 8 (2021) 71.
[4] H. Al-kuraishy, A.I. Al-Gareeb, N. Cruz-Martins, E.S. Batiha, The looming effects of estrogen in Covid-19: A Rocky Rollout, Front. Nutrition 8 (2021) 82.
[5] T. Sharma, M. Abohashrh, M.H. Baig, J.J. Dong, M.M. Alam, I. Ahmad, S. Irfan, Screening of drug databank against WT and mutant main protease of SARS-CoV-2: Towards finding potential compound for repurposing against COVID-19, Saudi J. Biol. Sci. (2021).
[6] H.M. Al-Kuraishy, N.R. Hussien, M.S. Al-Naimi, A.K. Al-Buhadily, A.I. Al-Gareeb, C. Lungnier, Renin-Angiotensin system and fibrinolytic pathway in COVID-19: One-way skepticism, Biomed. Biotechnol. Res. J. (BBRJ) 4 (5) (2020 Aug 1) 33.
[7] H.M. Al-Kuraishy, A.I. Al-Gareeb, M.S. Al-Niemi, A.K. Al-Buhadily, N.A. Al-Harchan, C. Lugnier, COVID-19 and phosphodiesterase enzyme type 5 inhibitors, J. Microscopy Ultrastruct. 8 (4) (2020) 141.
[8] B.J. Barnes, J.M. Adrover, A. Baxter-Stoltzfus, A. Borczuk, J. Cools-Lartigue, J. M. Crawford, J. Daßler-Plenker, P. Guerci, C. Huynh, J.S. Knight, M. Loda, Targeting potential drivers of COVID-19: Neutrophil extracellular traps, J. Exp. Med. 217 (6) (2020).
[9] C. Rosales, Neutrophil: a cell with many roles in inflammation or several cell types? Front. Physiol. 20 (9) (2018 Feb) 113.
[10] J.V. Camp, C.B. Jonsson, A role for neutrophils in viral respiratory disease, Front. Immunol. 12 (8) (2017 May) 550.
[11] T. Gan, Y. Yang, F. Hu, X. Chen, J. Zhou, Y. Li, Y. Xu, H. Wang, Y. Chen, M. Zhang, TLR3 regulated poly I: C-induced neutrophil extracellular traps and acute lung injury partly through p38 MAP kinase, Front. Microbiol. 21 (9) (2018 Dec) 3174.
[12] S. Hanada, M. Pirzadeh, K.Y. Carver, J.C. Deng, Respiratory viral infection-induced microbiome alterations and secondary bacterial pneumonia, Front. Immunol. 16 (9) (2018 Nov) 2640.
[13] E.E. Calore, D.E. Uip, N.M. Perez, Pathology of the swine-origin influenza A (H1N1) flu, Pathol.-Res. Pract. 207 (2) (2011 Feb 15) 86–90.
[14] M.F. Konig, F. Andrade, A critical reappraisal of neutrophil extracellular traps and NETosis mimics based on differential requirements for protein citrullination, Front. Immunol. 4 (7) (2016 Nov) 461.
[15] H. Yang, M.H. Biermann, J.M. Brauner, Y. Liu, Y. Zhao, M. Herrmann, New insights into neutrophil extracellular traps: mechanisms of formation and role in inflammation, Front. Immunol. 12 (7) (2016 Aug) 302.
[16] C.H. Hiroki, J.E. Toller-Kawahisa, M.J. Fumagalli, D.F. Colon, L. Figueiredo, B. A. Fonseca, R.F. Franca, F.Q. Cunha, Neutrophil extracellular traps effectively control acute chikungunya virus infection, Front. Immunol. 31 (10) (2020 Jan) 3108.
[17] V. Papayannopoulos, Neutrophil extracellular traps in immunity and disease, Nat. Rev. Immunol. 18 (2) (2018 Feb) 134.
[18] E. Lefrançais, B. Mallavia, H. Zhuo, C.S. Calfee, M.R. Looney, Maladaptive role of neutrophil extracellular traps in pathogen-induced lung injury, JCI Insight 3 (3) (2018).
[19] M.J. Raftery, P. Lalwani, E. Krautkrämer, T. Peters, K. Scharffetter-Kochanek, R. Krüger, J. Hofmann, K. Seeger, D.H. Krüger, G. Schönrich, β2 integrin mediates hantavirus-induced release of neutrophil extracellular traps, J. Exp. Med. 211 (7) (2014 Jun 30) 1485–1497.
[20] F.D. Barr, C. Ochsenbauer, C.R. Wira, M. Rodriguez-Garcia, Neutrophil extracellular traps prevent HIV infection in the female genital tract, Mucosal Immunol. 11 (5) (2018 Sep) 1420–1428.
[21] P.S. Souza, L.V. Barbosa, L.F. Diniz, G.S. da Silva, B.R. Lopes, P.M. Souza, G.C. de Araujo, D. Pessoa, J. de Oliveira, F.P. Souza, K.A. Toledo, Neutrophil extracellular traps possess anti-human respiratory syncytial virus activity: Possible interaction with the viral F protein, Virus Res. 2 (251) (2018 Jun) 68–77.
[22] P. Mistry, S. Nakabo, L. O'Neil, R.R. Goel, K. Jiang, C. Carmona-Rivera, S. Gupta, D.W. Chan, P.M. Carlucci, X. Wang, F. Naz, Transcriptomic, epigenetic, and functional analyses implicate neutrophil diversity in the pathogenesis of systemic lupus erythematosus, Proc. Natl. Acad. Sci. 116 (50) (2019 Dec 10) 25222–25228.
[23] D. Nakazawa, J. Desai, S. Steiger, S. Müller, S.K. Devarapu, S.R. Mulay, T. Iwakura, H.J. Anders, Activated platelets induce MLKL-driven neutrophil necroptosis and release of neutrophil extracellular traps in venous thrombosis, Cell Death Discovery 4 (1) (2018 Jun 28) 1.
[24] M. Hoeksema, S. Tripathi, M. White, L. Qi, J. Taubenberger, M. van Eijk, H. Haagsman, K.L. Hartshorn, Arginine-rich histones have strong antiviral activity for influenza A viruses, Innate Immunity 21 (7) (2015 Oct) 736–745.
[25] T. Saitoh, J. Komano, Y. Saitoh, T. Misawa, M. Takahama, T. Kozaki, T. Uehata, H. Iwasaki, H. Omori, S. Yamaoka, N. Yamamoto, Neutrophil extracellular traps mediate a host defense response to human immunodeficiency virus-1, Cell Host Microbe 12 (1) (2012 Jul 19) 109–116.
[26] R. Holani, A. Babbar, G.A. Blyth, F. Lopes, H. Jijon, D.M. McKay, M. D. Hollenberg, E.R. Cobo, Cathelicidin-mediated lipopolysaccharide signaling via intracellular TLR4 in colonic epithelial cells evokes CXCL8 production, Gut Microbes 12 (1) (2020 Nov 9) 1785802.
[27] J. Xu, X. Zhang, M. Monestier, N.L. Esmon, C.T. Esmon, Extracellular histones are mediators of death through TLR2 and TLR4 in mouse fatal liver injury, J. Immunol. 187 (5) (2011 Sep 1) 2626–2631.
[28] B. Cortjens, J.B. van Woensel, R.A. Bem, Neutrophil extracellular traps in respiratory disease: guided anti-microbial traps or toxic webs? Paediatr. Respir. Rev. 1 (21) (2017 Jan) 54–61.
[29] G. Schönrich, M.J. Raftery, Neutrophil extracellular traps go viral, Front. Immunol. 19 (7) (2016 Sep) 366.
[30] S. Jimeno, P.S. Ventura, J.M. Castellano, S.I. García-Adasme, M. Miranda, P. Touza, I. Lllana, A. López-Escobar, Prognostic implications of neutrophil-lymphocyte ratio in COVID-19, Europ. J. Clin. Investi. (2021) e13404.
[31] H.M. Al-Kuraishy, A.I. Al-Gareeb, K.J. Alzahrani, N. Cruz-Martins, G.E. Batiha, The potential role of neopterin in Covid-19: a new perspective, Mol. Cell. Biochem. 476 (11) (2021 Nov) 4161–4166.
[32] X. Zou, K. Chen, J. Zou, P. Han, J. Hao, Z. Han, Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection, Front. Med. 14 (2020) 185–192.
[33] H. Onohuean, H.M. Al-Kuraishy, A.I. Al-Gareeb, S. Qusti, E.M. Alshammari, G. E. Batiha, Covid-19 and development of heart failure: mystery and truth, Naunyn-Schmiedeberg's Arch. Pharmacol. 394 (10) (2021 Oct) 2013–2021.
[34] A. Java, A.J. Apicelli, M.K. Liszewski, A. Coler-Reilly, J.P. Atkinson, A.H. Kim, H. S. Kulkarni, The complement system in COVID-19: friend and foe? JCI Insight 5 (15) (2020).
[35] A. Yaqinuddin, J. Kashir, Novel therapeutic targets for SARS-CoV-2-induced acute lung injury: Targeting a potential IL-1β/neutrophil extracellular traps feedback loop, Med. Hypotheses 1 (143) (2020 Oct), 109906.
[36] A. Yaqinuddin, P. Kvietys, J. Kashir, COVID-19: Role of neutrophil extracellular traps in acute lung injury, Respiratory Investigat. (2020).
[37] D. Toor, A. Jain, S. Kalhan, H. Manocha, V.K. Sharma, P. Jain, V. Tripathi, H. Prakash, Tempering Macrophage plasticity for controlling SARS-CoV-2 infection for managing COVID-19 disease, Front. Pharmacol. 11 (2020).
[38] H.M. Al-Kuraishy, A.I. Al-Gareeb, S. Qusti, E.M. Alshammari, G.A. Gyebi, G. E. Batiha, Covid-19-Induced Dysautonomia: A Menace of Sympathetic Storm, ASN Neuro. 13 (2021), 17590914211057635.
[39] H.M. Al-Kuraishy, A.I. Al-Gareeb, L. Alkazmi, A. Alexiou, G.E. Batiha, Levamisole Therapy in COVID-19, Viral Immunol. (2021 Aug 12).
[40] J. Hazeldine, P. Harris, I.L. Chapple, M. Grant, H. Greenwood, A. Livesey, E. Sapey, J.M. Lord, Impaired neutrophil extracellular trap formation: a novel defect in the innate immune system of aged individuals, Aging Cell 13 (4) (2014 Aug) 690–698.
[41] B.N. Porto, R.T. Stein, Neutrophil extracellular traps in pulmonary diseases: too much of a good thing? Front. Immunol. 15 (7) (2016 Aug) 311.

[42] P. Winnersbach, J. Rossaint, E.M. Buhl, S. Singh, J. Lölsberg, M. Wessling, R. Rossaint, C. Bleilevens, Platelet count reduction during in vitro membrane oxygenation affects platelet activation, neutrophil extracellular trap formation and clot stability, but does not prevent clotting, Perfusion (2021), 0267659121989231.

[43] M. Godement, J. Zhu, C. Cerf, A. Vieillard-Baron, A. Maillon, B. Zuber, V. Bardet, G. Geri, Neutrophil Extracellular Traps in SARS-CoV2 related pneumonia in ICU patients: the NETCOV2 study, Front. Med. 8 (2021).

[44] Nawar R. Hussien, Marwa S. Al-Niemi, Hayder M. Al-Kuraishy, Ali I. Al-Grebe, Statins and Covid-19: The Neglected Front of bidirectional effects, J. Pak. Med. Assoc. (Suppl. 8) (2021).

[45] S.H. Twaddell, K.J. Baines, C. Grainge, P.G. Gibson, The emerging role of neutrophil extracellular traps in respiratory disease, Chest 156 (4) (2019 Oct 1) 774–782.

[46] J.J. Lai, F.M. Cruz, K.L. Rock, Immune sensing of cell death through recognition of histone sequences by C-type lectin-receptor-2d causes inflammation and tissue injury, Immunity 52 (1) (2020 Jan 14) 123–135.

[47] A. Arcanjo, J. Logullo, C.C. Menezes, T.C. Giangiarulo, M.C. Dos Reis, G.M. de Castro, F.Y. da Silva, A.R. Todeschini, L. Freire-de-Lima, D. Decoté-Ricardo, A. Ferreira-Pereira, The emerging role of neutrophil extracellular traps in severe acute respiratory syndrome coronavirus 2 (COVID-19), Sci. Rep. 10 (1) (2020 Nov 12) 1.

[48] G.E. Batiha, H.M. Shaheen, H.M. Al-Kuraishy, J.O. Teibo, O.A. Akinfe, A.I. Al-Garbee, T.K. Teibo, S.M. Kabrah, Possible mechanistic insights into iron homeostasis role of the action of 4-aminoquinolines (chloroquine/hydroxychloroquine) on COVID-19 (SARS-CoV-2) infection, Eur. Rev. Med. Pharmacol. Sci. 25 (2021 Dec) 7565–7584.

[49] L. Vanderbeke, P. Van Mol, Y. Van Herck, F. De Smet, S. Humblet-Baron, K. Martinod, A. Antoranz, I. Arijs, B. Boeckx, F.M. Bosisio, M. Casaer, Monocyte-Driven Atypical Cytokine Storm and Aberrant Neutrophil Activation as Key Mediators of COVID19 Disease Severity, Immunity (2020).

[50] H.M. Al-Kuraishy, A.I. Al-Gareeb, M. Alblihed, S.G. Guerreiro, N. Cruz-Martins, G. E. Batiha, COVID-19 in relation to hyperglycemia and diabetes mellitus, Front. Cardiovascular Med. 8 (2021).

[51] Q. Hu, H. Shi, T. Zeng, H. Liu, Y. Su, X. Cheng, J. Ye, Y. Yin, M. Liu, H. Zheng, X. Wu, Increased neutrophil extracellular traps activate NLRP3 and inflammatory macrophages in adult-onset Still's disease, Arthritis Res. Therapy 21 (1) (2019 Dec) 1.

[52] J. Wang, Q. Li, Y. Yin, Y. Zhang, Y. Cao, X. Lin, L. Huang, D. Hoffmann, M. Lu, Y. Qiu, Excessive neutrophils and neutrophil extracellular traps in COVID-19, Front. Immunol. 18 (11) (2020 Aug) 2063.

[53] W.J. Ouwendijk, M.P. Raadsen, J.J. van Kampen, R.M. Verdijk, J.H. von der Thusen, L. Guo, R.A. Hoek, J.P. van den Akker, H. Endeman, T. Langerak, R. Molenkamp, Neutrophil extracellular traps persist at high levels in the lower respiratory tract of critically ill COVID-19 patients, J. Infect. Dis. (2021 Jan 27).

[54] H.M. Al-Kuraishy, A.I. Al-Gareeb, S. Qusti, E.M. Alshammari, F.O. Atanu, G. E. Batiha, Arginine vasopressin and pathophysiology of COVID-19: An innovative perspective, Biomed. Pharmacother. 1 (143) (2021 Nov), 112193.

[55] S.F. Lax, K. Skok, P. Zechner, H.H. Kessler, N. Kaufmann, C. Koelblinger, K. Vander, U. Bargfrieder, M. Trauner, Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series, Ann. Intern. Med. 173 (5) (2020 Sep 1) 350–361.

[56] H.M. Al-Kuraishy, A.I. Al-Gareeb, N. Qusty, A. Alexiou, G.E. Batiha, Impact of Sitagliptin in Non-Diabetic Covid-19 Patients, Current Mol. Pharmacol. (2021 Sep 1).

[57] Y. Zuo, M. Zuo, S. Yalavarthi, K. Gockman, J.A. Madison, H. Shi, W. Woodard, S. P. Lezak, N.L. Lugogo, J.S. Knight, Y. Kanthi, Neutrophil extracellular traps and thrombosis in COVID-19, J. Thromb. Thrombolysis 51 (2) (2021 Feb) 446–453.

[58] Y. Hisada, S.P. Grover, A. Maqsood, R. Houston, C. Ay, D.F. Noubouossie, B. C. Cooley, H. Wallén, N.S. Key, C. Thålin, Á.Z. Farkas, Neutrophils and neutrophil extracellular traps enhance venous thrombosis in mice bearing human pancreatic tumors, Haematologica 105 (1) (2020 Jan) 218.

[59] E. Laridan, K. Martinod, S.F. De Meyer, Neutrophil extracellular traps in arterial and venous thrombosis, in: Seminars in thrombosis and hemostasis 2019, vol. 45, no. 1, Thieme Publishing, pp. 86-93.

[60] S.R. Clark, A.C. Ma, S.A. Tavener, B. McDonald, Z. Goodarzi, M.M. Kelly, K. D. Patel, S. Chakrabarti, E. McAvoy, G.D. Sinclair, E.M. Keys, Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood, Nat. Med. 13 (4) (2007 Apr) 463–469.

[61] H.M. Al-kuraishy, A.I. Al-Gareeb, F.O. Atanu, M.A. EL-Zamkan, H.M. Diab, A. S. Ahmed, T.J. Al-Maiahy, A.J. Obaidullah, S. Alshehri, M.M. Ghoniem, G. E. Batiha, Maternal Transmission of SARS-CoV-2: Safety of Breastfeeding in Infants Born to Infected Mothers, Front. Pediatrics 9 (2021).

[62] F.B. Belen-Apak, F. Sarıalioğlu, Pulmonary intravascular coagulation in COVID-19: possible pathogenesis and recommendations on anticoagulant/thrombolytic therapy, J. Thromb. Thrombolysis 50 (2) (2020 Aug) 278–280.

[63] H.M. Al-Kuraishy, A.I. Al-Gareeb, Acute kidney injury and COVID-19, Egypt. J. Int. Med. 33 (1) (2021 Dec) 1–5.

[64] A.R. Thierry, Does the newly observed inflammatory syndrome in children demonstrate a link between uncontrolled neutrophil extracellular traps formation and COVID-19? Pediatr. Res. 3 (2020 Jun) 1–2.

[65] P. Skendros, A. Mitsios, A. Chrysanthopoulou, D.C. Mastellos, S. Metallidis, P. Rafailidis, M. Ntinopoulou, E. Sertaridou, V. Tsironidou, C. Tsigalou, M. Tektonidou, Complement and tissue factor–enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis, J. Clin. Investig. 130 (11) (2020 Nov 2) 6151–6157.

[66] A.M. Risitano, D.C. Mastellos, M. Huber-Lang, D. Yancopoulou, C. Garlanda, F. Ciceri, J.D. Lambris, Complement as a target in COVID-19? Nat. Rev. Immunol. 20 (6) (2020 Jun) 343–344.

[67] E.M. Conway, Complement-coagulation connections, Blood Coagul. Fibrinolysis 29 (3) (2018 Apr 1) 243–251.

[68] S. Mastaglio, A. Ruggeri, A.M. Risitano, P. Angelillo, D. Yancopoulou, D. C. Mastellos, M. Huber-Lang, S. Piemontese, A. Assanelli, C. Garlanda, J. D. Lambris, The first case of COVID-19 treated with the complement C3 inhibitor AMY-101, Clinical Immunol. 1 (215) (2020 Jun), 108450.

[69] E. Gavriilaki, R.A. Brodsky, Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily, Br. J. Haematol. 189 (6) (2020 Jun) e227–e230.

[70] P.F. Stahel, S.R. Barnum, Complement inhibition in coronavirus disease (COVID)-19: a neglected therapeutic option, Front. Immunol. 7 (11) (2020 Jul) 1661.

[71] E.A. Middleton, X.Y. He, F. Denorme, R.A. Campbell, D. Ng, S.P. Salvatore, M. Mostyka, A. Baxter-Stoltzfus, A.C. Borczuk, M. Loda, M.J. Cody, Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome, Blood, J. Am. Soc. Hematol. 136 (10) (2020 Sep 3) 1169–1179.

[72] S. Oehmcke, M. Mörgelin, H. Herwald, Activation of the human contact system on neutrophil extracellular traps, J. Innate Immun. 1 (3) (2009) 225–230.

[73] K. Martinod, D.D. Wagner, Thrombosis: tangled up in NETs, Blood 123 (18) (2014) 2768.

[74] S. Massberg, L. Grahl, M.L. von Bruehl, D. Manukyan, S. Pfeiler, C. Goosmann, V. Brinkmann, M. Lorenz, K. Bidzhekov, A.B. Khandagale, I. Konrad, Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases, Nat. Med. 16 (8) (2010 Aug) 887–896.

[75] T.J. Gould, T.T. Vu, L.L. Swystun, D.J. Dwivedi, S.H. Mai, J.I. Weitz, P.C. Liaw, Neutrophil extracellular traps promote thrombin generation through platelet-dependent and platelet-independent mechanisms, Arterioscler. Thromb. Vasc. Biol. 34 (9) (2014 Sep) 1977–1984.

[76] Y. Wang, L. Luo, O.Ö. Braun, J. Westman, R. Madhi, H. Herwald, M. Mörgelin, H. Thorlacius, Neutrophil extracellular trap-microparticle complexes enhance thrombin generation via the intrinsic pathway of coagulation in mice, Sci. Rep. 8 (1) (2018 Mar 5) 1–4.

[77] M. Moubarak, K.I. Kasozi, H.F. Hetta, H.M. Shaheen, A. Rauf, H.M. Al-Kuraishy, S. Qusti, E.M. Alshammari, E.T. Ayikobua, F. Ssempijja, A.M. Afodun, The rise of SARS-CoV-2 variants and the role of convalescent plasma therapy for management of infections, Life. 11 (8) (2021 Aug) 734.

[78] H. Qi, S. Yang, L. Zhang, Neutrophil extracellular traps and endothelial dysfunction in atherosclerosis and thrombosis, Front. Immunol. 7 (8) (2017 Aug) 928.

[79] H.M. Al-Kuraishy, O.M. Sami, N.R. Hussain, A.I. Al-Gareeb, Metformin and/or vildagliptin mitigate type II diabetes mellitus induced-oxidative stress: the intriguing effect, J. Adv. Pharm. Technol. Res. 11 (3) (2020 Jul) 142.

[80] W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, L. Liu, H. Shan, C.L. Lei, D.S. Hui, B. Du, Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (18) (2020 Apr 30) 1708–1720.

[81] M.J. Kraakman, M.K. Lee, A. Al-Sharea, D. Dragoljevic, T.J. Barrett, E. Montenont, D. Basu, S. Heywood, H.L. Kammoun, M. Flynn, A. Whillas, Neutrophil-derived S100 calcium-binding proteins A8/A9 promote reticulated thrombocytosis and atherogenesis in diabetes, J. Clin. Investig. 127 (6) (2017 Jun 1) 2133–2147.

[82] J. Pérez-Galarza, C. Prócel, C. Cañadas, D. Aguirre, R. Pibaque, R. Bedón, F. Sempértegui, H. Drexhage, L. Baldeón, Immune Response to SARS-CoV-2 Infection in Obesity and T2D: Literature Review, Vaccines. 9 (2) (2021 Feb) 102.

[83] M.S. Al-Nami, H.M. Al-Kuraishy, A.I. Al-Gareeb, Impact of thioctic acid on glycemic indices and associated inflammatory-induced endothelial dysfunction in patients with type 2 diabetes mellitus: A case control study, Int. J. Crit. Illness Injury Sci. 10 (5) (2020 Sep 1) 21.

[84] L. Wang, X. Zhou, Y. Yin, Y. Mai, D. Wang, X. Zhang, Hyperglycemia induces neutrophil extracellular traps formation through an NADPH oxidase-dependent pathway in diabetic retinopathy, Front. Immunol. 8 (9) (2019 Jan) 3076.

[85] S. Suhail, J. Zajac, C. Fossum, H. Lowater, C. McCracken, N. Severson, B. Laatsch, A. Narkiewicz-Jodko, B. Johnson, J. Liebau, S. Bhattacharyya, Role of Oxidative Stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) Infection: A Review, Protein. J. 26 (2020 Oct) 1–3.

[86] L. Wu, A.M. O'Kane, H. Peng, Y. Bi, D. Motriuk-Smith, J. Ren, SARS-CoV-2 and cardiovascular complications: from molecular mechanisms to pharmaceutical management, Biochem. Pharmacol. 21 (2020 Jun), 114114.

[87] H.M. Al-Kuraishy, A.I. Al-Gareeb, G. Mostafa-Hedeab, K.I. Kasozi, G. Zirintunda, A. Aslam, M. Allahyani, S.C. Welburn, G.E. Batiha, Effects of β-Blockers on the Sympathetic and Cytokines Storms in Covid-19, Front. Immunol. 12 (2021).

[88] L. Aldabbous, V. Abdul-Salam, T. McKinnon, L. Duluc, J. Pepke-Zaba, M. Southwood, A.J. Ainscough, C. Hadinnapola, M.R. Wilkins, M. Toshner, B. Wojciak-Stothard, Neutrophil extracellular traps promote angiogenesis: evidence from vascular pathology in pulmonary hypertension, Arterioscler. Thromb. Vasc. Biol. 36 (10) (2016 Oct) 2078–2087.

[89] J. Li, D. Tong, Y. Wang, Y. Liu, X. Zhang, N. Liu, S. Wang, Y. Xu, Y. Li, X. Yin, W. Liu, Neutrophil extracellular traps enhance pro-coagulant activity in patients with essential hypertension, J. Thromb. Haemost. (2020 Dec 12).

[90] J.H. Li, D.X. Tong, Y. Wang, L. Gao, Y. Liu, X.H. Zhang, W.J. Chen, J.Y. Chi, N. Liu, K. Yang, S.P. Wang, Neutrophil extracellular traps exacerbate coagulation and endothelial damage in patients with essential hypertension and hyperhomocysteinemia, Thromb. Res. 1 (197) (2021 Jan) 36–43.

[91] Z. Zhou, S. Zhang, S. Ding, M. Abudupataer, Z. Zhang, X. Zhu, W. Zhang, Y. Zou, X. Yang, J. Ge, T. Hong, Excessive neutrophil extracellular trap formation aggravates acute myocardial infarction injury in apolipoprotein E deficiency mice via the ROS-dependent pathway, Oxidative Med. Cell. Longevity. 2019 (2019).
[92] K. Eghbalzadeh, L. Georgi, T. Louis, H. Zhao, U. Keser, C. Weber, M. Mollenhauer, A. Conforti, T. Wahlers, A. Paunel-Görgülü, Compromised anti-inflammatory action of neutrophil extracellular traps in PAD4-deficient mice contributes to aggravated acute inflammation after myocardial infarction, Front. Immunol. 1 (10) (2019 Oct) 2313.
[93] J.F. Wei, F.Y. Huang, T.Y. Xiong, Q. Liu, H. Chen, H. Wang, H. Huang, Y.C. Luo, X. Zhou, Z.Y. Liu, Y. Peng, Acute myocardial injury is common in patients with COVID-19 and impairs their prognosis, Heart 106 (15) (2020 Aug 1) 1154–1159.
[94] A. Bardají, A. Carrasquer, R. Sánchez-Giménez, N. Lal-Trehan, V. Del-Moral-Ronda, Ó.M. Peiró, G. Bonet, G. Castilho, I. Fort-Gallifa, C. Benavent, G. Recio, Prognostic implications of myocardial injury in patients with and without COVID-19 infection treated in a university hospital, Revista Española de Cardiología (English Edition) 74 (1) (2021 Jan 1) 24–32.
[95] M.S. Al-Niemi, H.M. Al-Kuraishy, A.I. Al-Gareeb, COVID-19 and risk of cardiomyocyte injury: The prevailing scenario, Current Med. Drug Res. 5 (2021) 211.
[96] N.G. Kounis, I. Koniari, C. Gogos, S.F. Assimakopoulos, Hypercoagulation and myocardial injury as risk factors for mortality in patients with COVID-19 pneumonia, Am. J. Emerg. Med. (2021).
[97] H.M. Al-Kuraishy, A.I. Al-Gareeb, A.K. Al-Buhadilly, Rosuvastatin improves vaspin serum levels in obese patients with acute coronary syndrome, Diseases 6 (1) (2018 Mar) 9.
[98] W. Dietz, C. Santos-Burgoa, Obesity and its implications for COVID-19 mortality, Obesity 28 (6) (2020) 1005.
[99] H.M. Al-Kuraishy, A.I. Al-Gareeb, Effect of orlistat alone or in combination with Garcinia cambogia on visceral adiposity index in obese patients, J. Intercultural Ethnopharmacol. 5 (4) (2016 Sep) 408.
[100] H. Wang, Q. Wang, J. Venugopal, J. Wang, K. Kleiman, C. Guo, D.T. Eitzman, Obesity-induced endothelial dysfunction is prevented by neutrophil extracellular trap inhibition, Sci. Rep. 8 (1) (2018 Mar 20) 1–7.
[101] I. Cichon, W. Ortmann, M. Santocki, M. Opydo-Chanek, E. Kolaczkowska, Scrutinizing Mechanisms of the 'Obesity Paradox in Sepsis': Obesity Is Accompanied by Diminished Formation of Neutrophil Extracellular Traps (NETs) Due to Restricted Neutrophil-Platelet Interactions, Cells. 10 (2) (2021 Feb) 384.
[102] A.N. Moorthy, K.B. Tan, S. Wang, T. Narasaraju, V.T. Chow, Effect of high-fat diet on the formation of pulmonary neutrophil extracellular traps during influenza pneumonia in BALB/c mice, Front. Immunol. 2 (7) (2016 Aug) 289.
[103] H.M. Al-Kuraishy, A.I. Al-Gareeb, H. Faidah, A. Alexiou, G.E. Batiha, Testosterone in COVID-19: An Adversary Bane or Comrade Boon. Frontiers in Cellular and Infection, Microbiology 832 (2021).
[104] M. D'Abbondanza, E.E. Martorelli, M.A. Ricci, S. De Vuono, E.N. Migliola, C. Godino, S. Corradetti, D. Siepi, M.T. Paganelli, N. Maugeri, G. Lupattelli, Increased plasmatic NETs by-products in patients in severe obesity, Sci. Rep. 9 (1) (2019 Oct 11) 1.
[105] M. Phelps, D.M. Christensen, T. Gerds, E. Fosbøl, C. Torp-Pedersen, M. Schou, L. Køber, K. Kragholm, C. Andersson, T. Biering-Sørensen, H.C. Christensen, Cardiovascular comorbidities as predictors for severe COVID-19 infection or death, Europ. Heart J.-Quality Care Clin. Outcomes 7 (2) (2021 Apr) 172–180.
[106] C.C. Yost, H. Schwertz, M.J. Cody, J.A. Wallace, R.A. Campbell, A. Vieira-de-Abreu, C.V. Araujo, S. Schubert, E.S. Harris, J.W. Rowley, M.T. Rondina, Neonatal NET-inhibitory factor and related peptides inhibit neutrophil extracellular trap formation, J. Clin. Investig. 126 (10) (2016 Oct 3) 3783–3798.
[107] R.A. Campbell, M. Cody, Y. Kosaka, H.D. Campbell, C. Yost, Placental HTRA1 Protease Cleaves Alpha-1-Antitrypsin and Generates Neonatal NET-Inhibitory Factor, Blood 132 (Supplement 1) (2018) 273.
[108] C.C. Yost, M.J. Cody, E.S. Harris, N.L. Thornton, A.M. McInturff, M.L. Martinez, N.B. Chandler, C.K. Rodesch, K.H. Albertine, C.A. Petti, A.S. Weyrich, Impaired neutrophil extracellular trap (NET) formation: a novel innate immune deficiency of human neonates, Blood 113 (25) (2009 Jun 18) 6419–6427.
[109] A. Tahamtan, S. Besteman, S. Samadizadeh, M. Rastegar, L. Bont, V. Salimi, Neutrophils in respiratory syncytial virus infection: From harmful effects to therapeutic opportunities, Br. J. Pharmacol. 178 (3) (2021 Feb) 515–530.
[110] K.R. Pertiwi, Potential Roles of Extracellular Traps in the Progression of Coronavirus Disease (Covid)-19, in: 7th International Conference on Research, Implementation, and Education of Mathematics and Sciences (ICRIEMS 2020), Atlantis Press, 2020, pp. 1–7, 2021 Mar 8.
[111] F. Di Costanzo, V. Di Dato, A. Ianora, G. Romano, Prostaglandins in marine organisms: A review, Mar. Drugs 17 (7) (2019 Jul) 428.
[112] V. Stojanovska, S.L. Miller, S.B. Hooper, G.R. Polglase, The Consequences of preterm birth and chorioamnionitis on brainstem respiratory centers: implications for neurochemical development and altered functions by inflammation and prostaglandins, Front. Cell. Neurosci. 1 (12) (2018 Feb) 26.
[113] K. Shishikura, T. Horiuchi, N. Sakata, D.A. Trinh, R. Shirakawa, T. Kimura, Y. Asada, H. Horiuchi, Prostaglandin E2 inhibits neutrophil extracellular trap formation through production of cyclic AMP, Br. J. Pharmacol. 173 (2) (2016 Jan) 319–331.
[114] R. Domingo-Gonzalez, G.J. Martínez-Colón, A.J. Smith, C.K. Smith, M. N. Ballinger, M. Xia, S. Murray, M.J. Kaplan, G.A. Yanik, B.B. Moore, Inhibition of neutrophil extracellular trap formation after stem cell transplant by prostaglandin E2, Am. J. Respir. Crit. Care Med. 193 (2) (2016 Jan 15) 186–197.
[115] P.S. Hair, A.I. Enos, N.K. Krishna, K.M. Cunnion, Inhibition of immune complex complement activation and neutrophil extracellular trap formation by peptide inhibitor of complement C1, Front. Immunol. 26 (9) (2018 Mar) 558.
[116] M. Hoxha, What about COVID-19 and arachidonic acid pathway? Eur. J. Clin. Pharmacol. 76 (11) (2020 Nov) 1501–1504.
[117] U.N. Das, Can bioactive lipids inactivate coronavirus (COVID-19)? Arch. Med. Res. 51 (3) (2020 Apr 1) 282–286.
[118] Y. Kondoh, A. Azuma, Y. Inoue, T. Ogura, S. Sakamoto, K. Tsushima, T. Johkoh, K. Fujimoto, K. Ichikado, Y. Matsuzawa, T. Saito, Thrombomodulin alfa for acute exacerbation of idiopathic pulmonary fibrosis. A randomized, double-blind placebo-controlled trial, Am. J. Respiratory Crit. Care Med. 201 (9) (2020) 1110–1119.
[119] J.L. Vincent, B. Francois, I. Zabolotskikh, M.K. Daga, J.B. Lascarrou, M.Y. Kirov, V. Pettilä, X. Wittebole, F. Meziani, E. Mercier, S.M. Lobo, Effect of a recombinant human soluble thrombomodulin on mortality in patients with sepsis-associated coagulopathy: the SCARLET randomized clinical trial, JAMA 321 (20) (2019 May 28) 1993–2002.
[120] Y. Shimomura, M. Suga, N. Kuriyama, T. Nakamura, T. Sakai, Y. Kato, Y. Hara, C. Yamashita, H. Nagasaki, M. Kaneki, O. Nishida, Recombinant human thrombomodulin inhibits neutrophil extracellular trap formation in vitro, J. Intensive Care 4 (1) (2016 Dec) 1–5.
[121] B. Shrestha, T. Ito, M. Kakuuchi, T. Totoki, T. Nagasato, M. Yamamoto, I. Maruyama, Recombinant thrombomodulin suppresses histone-induced neutrophil extracellular trap formation, Front. Immunol. 29 (10) (2019 Oct) 2535.
[122] N. Hayase, K. Doi, T. Hiruma, R. Matsuura, Y. Hamasaki, E. Noiri, M. Nangaku, N. Morimura, Recombinant thrombomodulin prevents acute lung injury induced by renal ischemia-reperfusion injury, Sci. Reports 10 (1) (2020) 1–2.
[123] M. Hultstrom, K. Fromell, A. Larsson, S.E. Quaggin, C. Betsholtz, R. Frithiof, M. Lipcsey, M. Jeansson, Elevated Angiopoietin-2 inhibits thrombomodulin-mediated anticoagulation in critically ill COVID-19 patients, medRxiv (2021).
[124] M. Mazzeffi, J.H. Chow, A. Amoroso, K. Tanaka, Revisiting the protein C pathway: an opportunity for adjunctive intervention in COVID-19? Anesth. Analg. (2020).
[125] L.D. Healy, C. Puy, J.A. Fernández, A. Mitrugno, R.S. Keshari, N.A. Taku, T. T. Chu, X. Xu, A. Gruber, F. Lupu, J.H. Griffin, Activated protein C inhibits neutrophil extracellular trap formation in vitro and activation in vivo, J. Biol. Chem. 292 (21) (2017 May 26) 8616–8629.
[126] W.L. Macias, S. Yan, M.D. Williams, S.L. Um, G.E. Sandusky, D.W. Ballard, J. M. Planquois, New insights into the protein C pathway: potential implications for the biological activities of drotrecogin alfa (activated), Crit. Care 9 (4) (2005 Aug) 1–8.
[127] J.H. Griffin, P. Lyden, COVID-19 hypothesis: Activated protein C for therapy of virus-induced pathologic thromboinflammation, Res. Pract. Thrombosis Haemostasis 4 (4) (2020 May) 506–509.
[128] G. Guglielmetti, M. Quaglia, P.P. Sainaghi, L.M. Castello, R. Vaschetto, M. Pirisi, F. Della Corte, G.C. Avanzi, P. Stratta, V. Cantaluppi, "War to the knife" against thromboinflammation to protect endothelial function of COVID-19 patients, Crit. Care 24 (1) (2020 Dec) 1–4.
[129] M. Panigada, N. Bottino, P. Tagliabue, G. Grasselli, C. Novembrino, V. Chantarangkul, A. Pesenti, F. Peyvandi, A. Tripodi, Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis, J. Thromb. Haemost. 18 (7) (2020 Jul) 1738–1742.
[130] A. Tabatabai, J. Rabin, J. Menaker, R. Madathil, S. Galvagno, A. Menne, J. H. Chow, A. Grazioli, D. Herr, K. Tanaka, T. Scalea, Factor VIII and functional protein c activity in critically ill patients with coronavirus disease 2019: a case series, A&a Pract. 14 (7) (2020 May), e01236.
[131] Y.N. Paudel, E. Angelopoulou, C. Piperi, V.R. Balasubramaniam, I. Othman, M. F. Shaikh, Enlightening the role of high mobility group box 1 (HMGB1) in inflammation: Updates on receptor signalling, Eur. J. Pharmacol. 5 (858) (2019 Sep), 172487.
[132] N. Maugeri, L. Campana, M. Gavina, C. Covino, M. De Metrio, C. Panciroli, L. Maiuri, A. Maseri, A. D'Angelo, M.E. Bianchi, P. Rovere-Querini, Activated platelets present high mobility group box 1 to neutrophils, inducing autophagy and promoting the extrusion of neutrophil extracellular traps, J. Thromb. Haemost. 12 (12) (2014 Dec) 2074–2088.
[133] R. Kang, Q. Zhang, W. Hou, Z. Yan, R. Chen, J. Bonaroti, P. Bansal, T.R. Billiar, A. Tsung, Q. Wang, D.L. Bartlett, Intracellular Hmgb1 inhibits inflammatory nucleosome release and limits acute pancreatitis in mice, Gastroenterology 146 (4) (2014 Apr 1) 1097–1107.
[134] M. Entezari, M. Javdan, D.J. Antoine, D.M. Morrow, R.A. Sitapara, V. Patel, M. Wang, L. Sharma, S. Gorasiya, M. Zur, W. Wu, Inhibition of extracellular HMGB1 attenuates hyperoxia-induced inflammatory acute lung injury, Redox Biol. 1 (2) (2014 Jan) 314–322.
[135] M.E. Street, HMGB1: a possible crucial therapeutic target for COVID-19? Hormone Res. Paediatrics 93 (2) (2020) 73–75.
[136] R. Chen, Y. Huang, J. Quan, J. Liu, H. Wang, T.R. Billiar, M.T. Lotze, H.J. Zeh, R. Kang, D. Tang, HMGB1 as a potential biomarker and therapeutic target for severe COVID-19, Heliyon 6 (12) (2020 Dec 1), e05672.
[137] J.J. DiNicolantonio, M. McCarty, J. Barroso-Aranda, Melatonin may decrease risk for and aid treatment of COVID-19 and other RNA viral infections, Open Heart 8 (2021) e001568, https://doi.org/10.1136/openhrt-2020-001568.
[138] A. Panagiotou, M. Trendelenburg, M. Osthoff, The lectin pathway of complement in myocardial ischemia/reperfusion injury—review of its significance and the potential impact of therapeutic interference by C1 esterase inhibitor, Front. Immunol. 25 (9) (2018 May) 1151.

[139] M. Wygrecka, D. Kosanovic, L. Wujak, K. Reppe, I. Henneke, H. Frey, M. Didiasova, G. Kwapiszewska, L.M. Marsh, N. Baal, H. Hackstein, Antihistone properties of C1 esterase inhibitor protect against lung injury, Am. J. Respir. Crit. Care Med. 196 (2) (2017 Jul 15) 186–199.
[140] I. Stroo, J. Yang, A.A. Anas, J.D. de Boer, G. van Mierlo, D. Roem, D. Wouters, R. Engel, J.J. Roelofs, C. van't Veer, T. van der Poll, Human plasma-derived C1 esterase inhibitor concentrate has limited effect on house dust mite-induced allergic lung inflammation in mice, PloS One 12 (10) (2017) e0186652.
[141] T.M. Thomson, E. Toscano-Guerra, E. Casis, R. Paciucci, C1 esterase inhibitor and the contact system in COVID-19, Br. J. Haematol. 190 (4) (2020 Aug) 520–524.
[142] P. Urwyler, P. Charitos, S. Moser, I.A. Heijnen, M. Trendelenburg, R. Thoma, J. Sumer, A. Camacho-Ortiz, M.R. Bacci, L.C. Huber, M. Stüssi-Helbling, Recombinant human C1 esterase inhibitor (conestat alfa) in the prevention of severe SARS-CoV-2 infection in hospitalized patients with COVID-19: A structured summary of a study protocol for a randomized, parallel-group, open-label, multi-center pilot trial (PROTECT-COVID-19), Trials. 22 (1) (2021 Dec) 1–3.
[143] H.M. Al-Kuraishy, A.I. Al-Gareeb, M.T. Naji, Brain natriuretic peptide in patients with acute ischemic stroke: role of statins, Biomed. Biotechnol. Res. J. (BBRJ) 4 (3) (2020 Jul 1) 239.
[144] J. Perdomo, H.H. Leung, Z. Ahmadi, F. Yan, J.J. Chong, F.H. Passam, B.H. Chong, Neutrophil activation and NETosis are the major drivers of thrombosis in heparin-induced thrombocytopenia, Nat. Commun. 10 (1) (2019 Mar 21) 1–4.
[145] N. Maugeri, G. De Gaetano, M. Barbanti, M.B. Donati, C. Cerletti, Prevention of platelet-polymorphonuclear leukocyte interactions: new clues to the anti-thrombotic properties of parnaparin, a low molecular weight heparin, Haematologica 90 (6) (2005) 833–839.
[146] J. Thachil, The versatile heparin in COVID-19, J. Thromb. Haemost. 18 (5) (2020 May) 1020–1022.
[147] D. White, S. MacDonald, T. Bull, M. Hayman, R. de Monteverde-Robb, D. Sapsford, A. Lavinio, J. Varley, A. Johnston, M. Besser, W. Thomas, Heparin resistance in COVID-19 patients in the intensive care unit, J. Thromb. Thrombolysis 50 (2020 Aug) 287–291.
[148] J.A. Hippensteel, W.B. LaRiviere, J.F. Colbert, C.J. Langouët-Astrié, E.P. Schmidt, Heparin as a therapy for COVID-19: current evidence and future possibilities, Am. J. Physiol.-Lung Cell. Mol. Physiol. 319 (2) (2020 Aug 1) L211–L217.
[149] B.Y. Fang, C.Y. Wang, C. Li, H.B. Wang, Y.D. Zhao, Amplified using DNase I and aptamer/graphene oxide for sensing prostate specific antigen in human serum, Sens. Actuators, B 1 (244) (2017 Jun) 928–933.
[150] X. Wang, S. Sun, Z. Duan, C. Yang, C. Chu, K. Wang, B. Liu, W. Ding, W. Li, J. Li, Protective effect of ethyl pyruvate on gut barrier function through regulations of ROS-related NETs formation during sepsis, Mol. Immunol. 1 (132) (2021 Apr) 108–116.
[151] A.G. Weber, A.S. Chau, M. Egeblad, B.J. Barnes, T. Janowitz, Nebulized in-line endotracheal dornase alfa and albuterol administered to mechanically ventilated COVID-19 patients: a case series, Mol. Med. 26 (1) (2020 Dec) 1–7.
[152] L. Blum, S. Schiffmann, M. Parnham, Immunomodulation by antibiotics. Fighting Antimicrobial Resistance, IAPC Publishing, Zagreb, Croatia, 2018.
[153] H.M. Al-Kuraishy, N.R. Hussien, M.S. Al-Naimi, A.K. Al-Buhadily, A.I. Al-Gareeb, C. Lungnier, Is ivermectin–Azithromycin combination the next step for COVID-19? Biomed. Biotechnol. Res. J. (BBRJ) 4 (5) (2020 Aug 1) 101.
[154] S. Kanoh, B.K. Rubin, Mechanisms of action and clinical application of macrolides as immunomodulatory medications, Clin. Microbiol. Rev. 23 (3) (2010 Jul 1) 590–615.
[155] J. Sultana, P.M. Cutroneo, S. Crisafulli, G. Puglisi, G. Caramori, G. Trifirò, Azithromycin in COVID-19 patients: pharmacological mechanism, clinical evidence and prescribing guidelines, Drug Saf. 43 (8) (2020 Aug) 691–698.
[156] H. Al-kuraishy, A.I. Al-Gareeb, N. Cruz-Martins, G.E. Batiha, Pleiotropic Effects of Tetracyclines in the Management of Covid-19: Emerging Perspectives, Front. Pharmacol. 12 (2021) 136.
[157] Z. Alqahtani, F. Jamali, Clinical outcomes of aspirin interaction with other non-steroidal anti-inflammatory drugs: a systematic review, J. Pharm. Pharm. Sci. 21 (1s) (2018 May 2) 48s–73s.
[158] S. Tacconelli, M. Dovizio, L. Di Francesco, A. Meneguzzi, I. D'Agostino, V. Evangelista, S. Manarini, M.L. Capone, L. Grossi, E. Porreca, C. Di Febbo, Reduced variability to aspirin antiplatelet effect by the coadministration of statins in high-risk patients for cardiovascular disease, Clin. Pharmacol. Ther. 104 (1) (2018 Jul) 111–119.
[159] C. Becattini, G. Agnelli, Aspirin for prevention and treatment of venous thromboembolism, Blood Rev. 28 (3) (2014 May 1) 103–108.
[160] A. Caudrillier, K. Kessenbrock, B.M. Gilliss, J.X. Nguyen, M.B. Marques, M. Monestier, P. Toy, Z. Werb, M.R. Looney, Platelets induce neutrophil extracellular traps in transfusion-related acute lung injury, J. Clin. Investig. 122 (7) (2012 Jul 2) 2661–2671.
[161] J. Tilgner, K.T. von Trotha, A. Gombert, M.J. Jacobs, M. Drechsler, Y. Döring, O. Soehnlein, J. Grommes, Aspirin, but not tirofiban displays protective effects in endotoxin induced lung injury, PLoS ONE 11 (9) (2016 Sep 1), e0161218.
[162] M.J. Lapponi, A. Carestia, V.I. Landoni, L. Rivadeneyra, J. Etulain, S. Negrotto, R. G. Pozner, M. Schattner, Regulation of neutrophil extracellular trap formation by anti-inflammatory drugs, J. Pharmacol. Exp. Ther. 345 (3) (2013 Jun 1) 430–437.
[163] J.H. Chow, A.K. Khanna, S. Kethireddy, D. Yamane, A. Levine, A.M. Jackson, M. T. McCurdy, A. Tabatabai, G. Kumar, P. Park, I. Benjenk, Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019, Anesth. Analg. 132 (4) (2021 Apr 1) 930–941.
[164] A.R. Thierry, B. Roch, SARS-CoV2 may evade innate immune response, causing uncontrolled neutrophil extracellular traps formation and multi-organ failure, Clin. Sci. 134 (12) (2020 Jun) 1295–1300.
[165] K. Iwata, A. Doi, G. Ohji, H. Oka, Y. Oba, K. Takimoto, W. Igarashi, D. H. Gremillion, T. Shimada, Effect of neutrophil elastase inhibitor (sivelestat sodium) in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): a systematic review and meta-analysis, Intern. Med. 49 (22) (2010) 2423–2432.
[166] A. Sakashita, Y. Nishimura, T. Nishiuma, K. Takenaka, K. Kobayashi, Y. Kotani, M. Yokoyama, Neutrophil elastase inhibitor (sivelestat) attenuates subsequent ventilator-induced lung injury in mice, Eur. J. Pharmacol. 571 (1) (2007 Sep 24) 62–71.
[167] N. Okayama, Y. Kakihana, D. Setoguchi, T. Imabayashi, T. Omae, A. Matsunaga, Y. Kanmura, Clinical effects of a neutrophil elastase inhibitor, sivelestat, in patients with acute respiratory distress syndrome, J. Anesthesia 20 (1) (2006 Feb) 6–10.
[168] S. Miyoshi, R. Ito, H. Katayama, K. Dote, M. Aibiki, H. Hamada, T. Okura, J. Higaki, Combination therapy with sivelestat and recombinant human soluble thrombomodulin for ARDS and DIC patients, Drug Des., Dev. Therapy 8 (2014) 1211.
[169] A. Sahebnasagh, F. Saghafi, M. Safdari, M. Khataminia, A. Sadremomtaz, H. R. Ghaleno, M. Bagheri, M.S. Bagheri, S. Habtemariam, R. Avan, Neutrophil Elastase Inhibitor (Sivelestat), may be a Promising Therapeutic Option for Management of Acute Lung Injury/Acute Respiratory Distress Syndrome or Disseminated Intravascular Coagulation in COVID-19, Authorea Preprints (2020).
[170] M.M. Mohamed, I.A. El-Shimy, M.A. Hadi, Neutrophil Elastase Inhibitors: A potential prophylactic treatment option for SARS-CoV-2-induced respiratory complications? 24 (2020) 311. https://doi.org/10.1186/s13054-020-03023-0.
[171] U.S. Kosgodage, R.P. Trindade, P.R. Thompson, J.M. Inal, S. Lange, Chloramidine/bisindolylmaleimide-I-mediated inhibition of exosome and microvesicle release and enhanced efficacy of cancer chemotherapy, Int. J. Mol. Sci. 18 (5) (2017 May) 1007.
[172] Y. Zhang, Y. Yin, S. Kuai, Z. Shan, H. Pei, J. Wang, Combination of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as diagnostic biomarker for rheumatoid arthritis, Int. J. Clin. Exp. Med. 9 (11) (2016 Jan 1) 22076–22081.
[173] M. Li, C. Lin, H. Deng, J. Strnad, L. Bernabei, D.T. Vogl, J.J. Burke, Y. Nefedova, A novel peptidylarginine deiminase 4 (PAD4) inhibitor BMS-P5 blocks formation of neutrophil extracellular traps and delays progression of multiple myeloma, Mol. Cancer Ther. 19 (7) (2020 Jul 1) 1530–1538.
[174] F. Izzo, M. Montella, A.P. Orlando, G. Nasti, G. Beneduce, G. Castello, F. Cremona, C.M. Ensor, F.W. Holtzberg, J.S. Bomalaski, M.A. Clark, Pegylated arginine deiminase lowers hepatitis C viral titers and inhibits nitric oxide synthesis, J. Gastroenterol. Hepatol. 22 (1) (2007 Jan) 86–91.
[175] M. Du, L. Yang, J. Gu, J. Wu, Y. Ma, T. Wang, Inhibition of Peptidyl Arginine Deiminase-4 Prevents Renal Ischemia-Reperfusion-Induced Remote Lung Injury, Mediators Inflamm. 30 (2020 Dec) 2020.
[176] K. Janiuk, E. Jabłońska, M. Garley, Significance of NETs Formation in COVID-19, Cells. 10 (1) (2021 Jan) 151.
[177] G.E. Batiha, Cyclosporine Attenuates Covid-19: Ensnare or Victory, Ann. Clin. Med. Case Rep. 7 (4) (2021) 1–8.
[178] A.K. Gupta, S. Giaglis, P. Hasler, S. Hahn, Efficient neutrophil extracellular trap induction requires mobilization of both intracellular and extracellular calcium pools and is modulated by cyclosporine A, PLoS ONE 9 (5) (2014 May 12), e97088.
[179] E. Tourneur, S.B. Mkaddem, C. Chassin, M. Bens, J.M. Goujon, N. Charles, C. Pellefigues, M. Aloulou, A. Hertig, R.C. Monteiro, S.E. Girardin, Cyclosporine A impairs nucleotide binding oligomerization domain (Nod1)-mediated innate antibacterial renal defenses in mice and human transplant recipients, PLoS Pathog. 9 (1) (2013 Jan 31), e1003152.
[180] E. Cure, A. Kucuk, C.M. Cumhur, Cyclosporine therapy in cytokine storm due to coronavirus disease 2019 (COVID-19), Rheumatol. Int. 40 (2020 Jul) 1177–1179.
[181] D.J. Morré, Preferential inhibition of the plasma membrane NADH oxidase (NOX) activity by diphenyleneiodonium chloride with NADPH as donor, Antioxid. Redox Signal. 4 (1) (2002 Feb 1) 207–212.
[182] M. Ostafin, M.P. Pruchniak, O. Ciepiela, A.Z. Reznick, U. Demkow, Different procedures of diphenyleneiodonium chloride addition affect neutrophil extracellular trap formation, Anal. Biochem. 15 (509) (2016 Sep) 60–66.
[183] M. Rastogi, S.K. Singh, Zika virus NS1 affects the junctional integrity of human brain microvascular endothelial cells, Biochimie 1 (176) (2020 Sep) 52–61.
[184] Y.J. Youn, Y.B. Lee, S.H. Kim, H.K. Jin, J.S. Bae, C.W. Hong, Nucleocapsid and Spike Proteins of SARS-CoV-2 Drive Neutrophil Extracellular Trap Formation, Immune Network. 3 (2020 Dec) 21.
[185] H.M. Al-Kuraishy, A.I. Al-Gareeb, H.J. Waheed, T.J. Al-Maiahy, Differential effect of metformin and/or glyburide on apelin serum levels in patients with type 2 diabetes mellitus: Concepts and clinical practice, J. Adv. Pharm. Technol. Res. 9 (3) (2018 Jul) 80.
[186] M.H. Abdul-Hadi, M.T. Naji, H.A. Shams, O.M. Sami, N.A. Al-Harchan, H.M. Al-Kuraishy, A.I. Al-Gareeb, Oxidative stress injury and glucolipotoxicity in type 2 diabetes mellitus: The potential role of Metformin and sitagliptin, Biomed. Biotechnol. Res. J. (BBRJ) 4 (2) (2020 Apr 1) 166.
[187] H. Wang, T. Li, S. Chen, Y. Gu, S. Ye, Neutrophil extracellular trap mitochondrial DNA and its autoantibody in systemic lupus erythematosus and a proof-of-concept trial of Metformin, Arthritis Rheumatol. 67 (12) (2015 Dec) 3190–3200.
[188] P. Luo, L. Qiu, Y. Liu, X.L. Liu, J.L. Zheng, H.Y. Xue, W.H. Liu, D. Liu, J. Li, Metformin treatment was associated with decreased mortality in COVID-19

patients with diabetes in a retrospective analysis, Am. J. Tropical Med. Hygiene 103 (1) (2020 Jul 8) 69–72.
[189] C. Ponticelli, G. Moroni, Hydroxychloroquine in systemic lupus erythematosus (SLE), Expert Opinion Drug Saf. 16 (3) (2017 Mar 4) 411–419.
[190] Y. Chen, Y.L. Traore, S. Yang, J. Lajoie, K.R. Fowke, D.W. Rickey, E.A. Ho, Implant delivering hydroxychloroquine attenuates vaginal T lymphocyte activation and inflammation, J. Control. Release 10 (277) (2018 May) 102–113.
[191] R.G. Espinola, S.S. Pierangeli, A.E. Ghara, E.N. Harris, Hydroxychloroquine reverses platelet activation induced by human IgG anti-phospholipid antibodies, Thromb. Haemost. 87 (03) (2002) 518–522.
[192] C. Belizna, Hydroxychloroquine as an anti-thrombotic in antiphospholipid syndrome, Autoimmun. Rev. 14 (4) (2015 Apr 1) 358–362.
[193] S. Zhang, Q. Zhang, F. Wang, X. Guo, T. Liu, Y. Zhao, B. Gu, H. Chen, Y. Li, Hydroxychloroquine inhibiting neutrophil extracellular trap formation alleviates hepatic ischemia/reperfusion injury by blocking TLR9 in mice, Clin. Immunol. 1 (216) (2020 Jul), 108461.
[194] B.A. Boone, P. Murthy, J. Miller-Ocuin, W.R. Doerfler, J.T. Ellis, X. Liang, M. A. Ross, C.T. Wallace, J.L. Sperry, M.T. Lotze, M.D. Neal, Chloroquine reduces hypercoagulability in pancreatic cancer through inhibition of neutrophil extracellular traps, BMC Cancer 18 (1) (2018 Dec) 1–2.
[195] A.K. Singh, A. Singh, A. Shaikh, R. Singh, A. Misra, Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries, Diabetes Metabolic Syndrome: Clin. Res. Rev. 14 (3) (2020 May 1) 241–246.
[196] A. Gasmi, M. Peana, S. Noor, R. Lysiuk, A. Menzel, A.G. Benahmed, G. Bjørklund, Chloroquine and hydroxychloroquine in the treatment of COVID-19: the never-ending story, Appl. Microbiol. Biotechnol. 30 (2021 Jan) 1.
[197] G. Aldini, A. Altomare, G. Baron, G. Vistoli, M. Carini, L. Borsani, F. Sergio, N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why, Free Radical Res. 52 (7) (2018 Jul 3) 751–762.
[198] A. Le Joncour, R. Martos, S. Loyau, N. Lelay, A. Dossier, A. Cazes, P. Fouret, F. Domont, T. Papo, M. Jandrot-Perrus, M.C. Bouton, Critical role of neutrophil extracellular traps (NETs) in patients with Behcet's disease, Ann. Rheum. Dis. 78 (9) (2019 Sep 1) 1274–1282.
[199] B.M. Craver, G. Ramanathan, S. Hoang, X. Chang, L.F. Mendez Luque, S. Brooks, H.Y. Lai, A.G. Fleischman, N-acetylcysteine inhibits thrombosis in a murine model of myeloproliferative neoplasm, Blood Adv. 4 (2) (2020 Jan 28) 312–321.
[200] H. Ibrahim, A. Perl, D. Smith, T. Lewis, Z. Kon, R. Goldenberg, K. Yarta, C. Staniloae, M. Williams, Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine, Clin. Immunol. 1 (219) (2020 Oct), 108544.
[201] A. Andreou, S. Trantza, D. Filippou, N. Sipsas, S. Tsiodras, COVID-19: The potential role of copper and N-acetylcysteine (NAC) in a combination of candidate antiviral treatments against SARS-CoV-2, In vivo 34 (3 suppl) (2020) 1567–1588.
[202] F. Sassi, C. Tamone, P. D'Amelio, Vitamin D: nutrient, hormone, and immunomodulator, Nutrients. 10 (11) (2018 Nov) 1656.
[203] K. Amrein, M. Scherkl, M. Hoffmann, S. Neuwersch-Sommeregger, M. Köstenberger, A.T. Berisha, G. Martucci, S. Pilz, O. Malle, Vitamin D deficiency 2.0: an update on the current status worldwide, Eur. J. Clin. Nutr. 74 (11) (2020 Nov) 1498–1513.
[204] I. Buondonno, G. Rovera, F. Sassi, M.M. Rigoni, C. Lomater, S. Parisi, R. Pellerito, G.C. Isaia, P. D'Amelio, Vitamin D and immunomodulation in early rheumatoid arthritis: A randomized double-blind placebo-controlled study, PLoS ONE 12 (6) (2017 Jun 5), e0178463.
[205] N. Vyas, S.J. Kurian, D. Bagchi, M.K. Manu, K. Saravu, M.K. Unnikrishnan, C. Mukhopadhyay, M. Rao, S.S. Miraj, Vitamin D in prevention and treatment of COVID-19: current perspective and future prospects, J. Am. Coll. Nutr. 16 (2020 Aug) 1–4.
[206] C.F. Urban, J.E. Nett, in: Neutrophil extracellular traps in fungal infection. InSeminars in cell & developmental biology, Academic Press, 2019, pp. 47–57.
[207] J.D. Rocha, M.T. Nascimento, D. Decote-Ricardo, S. Côrte-Real, A. Morrot, N. Heise, M.P. Nunes, J.O. Previato, L. Mendonça-Previato, G.A. DosReis, E. M. Saraiva, Capsular polysaccharides from Cryptococcus neoformans modulate production of neutrophil extracellular traps (NETs) by human neutrophils, Sci. Rep. 5 (1) (2015 Jan 26) 1.
[208] A.B. Guimarães-Costa, M.T. Nascimento, G.S. Froment, R.P. Soares, F. N. Morgado, F. Conceição-Silva, E.M. Saraiva, Leishmania amazonensis promastigotes induce and are killed by neutrophil extracellular traps, Proc. Natl. Acad. Sci. 106 (16) (2009 Apr 21) 6748–6753.
[209] D.A. Rodrigues, E.B. Prestes, A.M. Gama, L.D. Silva, A.A. Pinheiro, J.M. Ribeiro, R.M. Campos, P.M. Pimentel-Coelho, H.S. De Souza, A. Dicko, P.E. Duffy, CXCR4 and MIF are required for neutrophil extracellular trap release triggered by Plasmodium-infected erythrocytes, PLoS Pathog. 16 (8) (2020 Aug 14), e1008230.
[210] K.C. Malcolm, S.M. Caceres, K. Pohl, K.R. Poch, A. Bernut, L. Kremer, D. L. Bratton, J.L. Herrmann, J.A. Nick, Neutrophil killing of Mycobacterium abscessus by intra-and extracellular mechanisms, PLoS ONE 13 (4) (2018 Apr 19), e0196120.
[211] E.H. Fahad, M.S. Al-Niemi, N.R. Hussain, H.M. Al-Kuraishy, A.I. Al-Gareeb, Hypertension Severity and Inflammatory Burden as Evaluated by Neutrophil-Lymphocyte Ratio: Role of Telmisartan, Int. J. Nutrit., Pharmacol., Neurol. Dis. 11 (4) (2021 Oct 1) 274.
[212] H.M. Al-Kuraishy, A.I. Al-Gareeb, K.J. Alzahrani, A. Alexiou, G.E. Batiha, Niclosamide for Covid-19: bridging the gap, Mol. Biol. Rep. 48 (12) (2021 Dec) 8195–8202.
[213] G.E. Batiha, A.I. Al-Gareeb, S. Qusti, E.M. Alshammari, D. Rotimi, O.S. Adeyemi, H.M. Al-kuraishy, Common NLRP3 inflammasome inhibitors and Covid-19: Divide and Conquer, Sci. African (2021) e01084.