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Commentary

Targeting Neprilysin (NEP) pathways: A potential new hope to defeat COVID-19 ghost

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ABSTRACT

COVID-19 is an ongoing viral pandemic disease that is caused by SARS-CoV2, inducing severe pneumonia in humans. However, several classes of repurposed drugs have been recommended, no specific vaccines or effective therapeutic interventions for COVID-19 are developed till now. Viral dependence on ACE-2, as entry receptors, drove the researchers into RAS impact on COVID-19 pathogenesis. Several evidences have pointed at Neprilysin (NEP) as one of pulmonary RAS components. Considering the protective effect of NEP against pulmonary inflammatory reactions and fibrosis, it is suggested to direct the future efforts towards its potential role in COVID-19 pathophysiology. Thus, the review aimed to shed light on the potential beneficial effects of NEP pathways as a novel target for COVID-19 therapy by summarizing its possible molecular mechanisms. Additional experimental and clinical studies explaining more the relationships between NEP and COVID-19 will greatly benefit in designing the future treatment approaches.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious viral disease that is caused by a newly discovered coronavirus, namely severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. It is a virus belonging to order Nidovirales of family Coronaviridae, which are single-stranded RNA viruses [2] and broadly distributed in both humans and other mammals [3].

Majority of the people infected with 2019 novel coronavirus (2019-nCoV) may recover without requiring special treatment [4], except the elderly people and those with some medical problems such as hypertension, diabetes [5] and chronic respiratory disease [6]. Such patients are more liable to be infected with COVID-19 and might develop a fatal pneumonia with clinical presentation greatly resembling that caused by the previous beta-coronavirus SARS-COV appeared in 2003; severe acute respiratory syndrome (SARS) [7].

In such cohort, patients firstly complain of fever, dry cough, and at late stage, may suffer from dyspnea that makes them in a desperate need of intensive care unit (ICU) admission and oxygen therapy [8]. However, the time between ICU admission and ARDS development is recorded to be as short as 2 days [9], being the reason for the high mortality rate associated with COVID-19 at this stage [10].

Till present, no COVID-19-specific vaccines or medications are available, although some national medical authorities recommend testing the efficacy of antiviral medication in especially sever clinical trials [11]. In addition, several medical researchers suggest starting the

Abbreviations: ACE, Angiotensin-converting enzyme; ACEI, ACE inhibitors; AD, Alzheimer's disease; ALI/ARDS, Acute lung injury/Acute respiratory distress syndrome; Ang, Angiotensin; ARBs, Angiotensin receptor blockers; AT1R, Angiotensin II receptor type 1; AT2R, Angiotensin II receptor type 2; Aβ, β-amyloid; BKs, Bradykinins; BR, Bradykinin receptor; COVID-19, Coronavirus disease 2019; CQ/HCQ, Chloroquine/Hydroxychloroquine; ECs, Endothelial cells; ET-1, Endothelin-1; eNOS, endothelial Nitric oxide synthase; fMLP, formyl Methionyl-meucyl-proline; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GPCR, G protein-coupled; GRP, Gastrin-releasing peptide; HO-1, Heme oxygenase-1; IL, Interleukin; MAPK/ERK, Mitogen-activated protein kinases/ Extracellular signal-regulated kinases; MasR, Mas receptor; MCP-1, Monocyte chemoattractant protein-1; MERS, Middle East Respiratory Syndrome; NADPH, Nicotinamide adenine dinucleotide phosphate (reduced form); NEP, Neprilysin; NEPi, Neprilysin inhibitors; NF-kB, Nuclear factor kappa B; NO, Nitric oxide; NPs, Natriuretic peptides; Nrf2, Nuclear factor erythroid 2–related factor 2; NSAIDs, Non steroidal anti-inflammatory drugs; PLCb/IP3, Phospholipase C beta/inositol trisphosphate; PNECs, Pulmonary neuroendocrine cells; PPARs, Peroxisome proliferator activator receptors; RAS, Renin angiotensin system; ROS, Reactive oxygen species; SARS-CoV, Severe acute respiratory syndrome coronavirus; SERMs, Selective estrogen receptor modulators; STZ, Streptozotocin; TGF-β1, Transforming growth factor- β1; TNF, Tumor necrosis factor; VEGF, Vascular endothelial growth factor

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supportive and symptomatic treatment till the new medications are developed [12,13].

Early evidences have shown that the pathogenicity for COVID-19 may be enhanced with increased the body susceptibility to induce a phenomenon called cytokine storm, in which the immune system gears up by overreacting and producing more inflammatory mediators to fight the infection [14]. As a result, a severe inflammatory reaction is produced accompanied with significant damage, including organ failure [15,16].

In view of cytokines storm caused by COVID-19 infection, high amounts of proinflammatory cytokines (e.g. IL-1β, IL-6, TNF-α, VEGF, GM-CSF and MCP-1) are detected [10], probably leading to associated pulmonary inflammation that can drive fibrosis in the injured tissues [17].

In addition to the dysregulated lung inflammation, emerging research and clinical studies increasingly indicate an alternative point of view for COVID-19 pathogenesis. They suggest that extreme lung tissue injury in COVID-19 may be attributed to vascular endothelial dysfunction, associated with subsequent activation, accumulation of platelets, and then, thrombus formation at the injured site [18,19], developing a stroke which is suggested to be the leading cause of death in-between sever COVID-19 cases [20].

Lymphocytopenia, a common striking finding in acute infections, is suggested to be a significant indicator of COVID-19 severity [16]. However, this decrease in lymphocytes count is noticed in both severe and non-severe COVID-19 patients [21], expecting that there may be another critical factor driving the development and deterioration of the disease. The most supportive observation now is the disclosure of higher neutrophil–lymphocyte-ratio (NLR) in COVID-19 severe patients than others [22]. Moreover, COVID-19 patients' laboratory examinations recently show thrombocytopenia, indicating the association of platelet-to-lymphocyte ratio (PLR) with COVID-19 progression and prognosis [23].

Given that the pulmonary tissue damage and microvascular injury recorded in COVID-19 patients is mainly caused by uncontrolled inflammatory reactions and its associated pro-thrombotic conditions, inhibiting the release of underlying inflammatory cytokines may be of great importance [24]. Hence, many studies targeted the utilization of some immunomodulatory agents including hydroxy chloroquine and corticosteroids as COVID-19 therapies to minimize the disease severity [22]. However, that therapeutic direction may interfere with the body immune system to efficiently act as a defense weapon against any other infections [25,26].

Simultaneously, many studies emphasized on the exploitation of COVID-19 virus to the angiotensin converting enzyme-2 (ACE-2) found on the host pulmonary system as entry receptors [27]; disrupting, of course, the normal physiological function of ACE-2/Ang (1–7)/MasR axis of the renin–angiotensin system (RAS) pathway [28].

Therefore, researchers suggested that the use of angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs), may show a positive trend towards the severe inflammatory reactions and endothelial dysfunction caused by stimulating the function of ACE/Ang II/AT-1 axis and thereby, towards the bad pulmonary effects associated with the COVID-19 infection [29,30]. However, no clinical trial, till this time, has been proved its efficacy in preventing or even reducing the COVID-19 severity [31,32].

Pursuing clinical trials with the absence of whole data describing the structure of COVID-19 virus and its related mechanisms may lead to unsatisfied outcomes. As well, understanding such data will greatly help in determining the most appropriate effective treatment protocols. Consequently, the first step to prevent and slow down the disease progression should involve the deduction of proper pathophysiology of that novel viral disease.

Identifying ACE-2 as a viral entry receptor will emphasize on the important role of classical RAS pathway in COVID-19 pathophysiology, however, neither the link between ACE-2 and other RAS components nor their exact roles in the COVID-19 pathogenesis have been neatly studied till now.

One RAS component, namely neprilysin (NEP), has been established to potentiate the physiological beneficial role ascribed to the ACE-2/ang (1–7)/MasR axis; by an alternative pathway [33]. Nowadays, NEP has emerged as a pharmaceutical target for many drugs; especially those used in treating cardiovascular diseases and Alzheimer's disease (AD) [34,35].

Considering the respiratory system, NEP was reported to play a vital role in protecting lungs from inflammation and fibrosis [36–38]. A long time ago, Borson et al.,1989 mentioned that rats infected with common respiratory tract pathogens, such as parainfluenza virus type-1, rat coronavirus, and Mycoplasma pulmonis showed low NEP activity; resulting in an increase in their susceptibility to inflammatory responses [39]. However, the precise NEP's role against life-threatening lung injuries has not been investigated yet.

Consequently, this current review aims to examine the cellular signaling pathways involving NEP in COVID-19 pathogenesis and to summarize the evidences supporting the potential beneficial effects of NEP as a novel target for therapy.

2. COVID-19 virus structure and disease pathophysiology

All previous and recent studies agreed with the fact that the surface of all human pathogenic coronaviruses is covered with crown like projections called spike (S) glycoproteins; giving the viruses their name [40]. In addition to S protein, another three main structural proteins have been recognized in SARS-CoV-2, namely envelope (E), nucleocapsid (N) and membrane (M) proteins [41], Fig. 1.

Specifically, S proteins are very important for SARS-CoV-2 infection to get started [42]. They possess two functional subunits by which the virus can enter into its target host cells involving; S1 subunit, which enables it to bind with receptors on the host cell surface and S2 subunit, that allows the virus to fuse into the cellular membrane [43].

Unlike other coronaviruses, several experimental analyses proved that SARS-CoV-2 does not use the common known viral entry receptors, such as aminopeptidase N (APN) [41] and dipeptidyl peptidase 4 (DPP4) [44], but, instead, can utilize ACE-2 receptor [27].

Additionally, it was revealed that transmembrane protease serine 2 (TMPRSS2) is very critical for the host cell entry of SARS-CoV-2 [45] and its plasma membrane fusion [46] resembling SARS-CoV [47]. Firstly, the virus starts its destructive journey with binding of S1 subunit to ACE-2 enzyme receptor on the cell membrane surface, which in turn activates TMPRSS2. Activation of TMPRSS2 is followed by cleavage of both virus's S1 subunits from its S2 subunits and so of the ACE-2 receptors. Secondly, activated TMPRSS2 can also act on the S2 subunit, activating it through prompting an irreversible conformational change that will facilitate the virus-cell fusion [48,49].

Within this view, understanding the precise involvement ACE-2, as a member of pulmonary RAS pathway, in COVID-19 pathophysiology may open new therapeutic possibilities for management.

3. Pulmonary Renin–Angiotensin system (RAS) and COVID-19

3.1. RAS overview

For years, RAS was depicted as a hormonal circulating system involved in fluid and electrolyte balance, systemic vascular resistance and blood pressure regulation [50,51]. However, a wealth of data showed that lung epithelial cells, fibroblasts and alveolar macrophages could also express the major constituents of the RAS [52,53] supporting the existence of a "local" pulmonary RAS that can be differentiated from the "systemic" circulating RAS [54].

As regards "local" RAS in the lung, it has been reported to involve multiple cellular mechanisms affecting the vascular permeability, fibroblast activity and alveolar epithelial cells [55,56]. By the time, it is

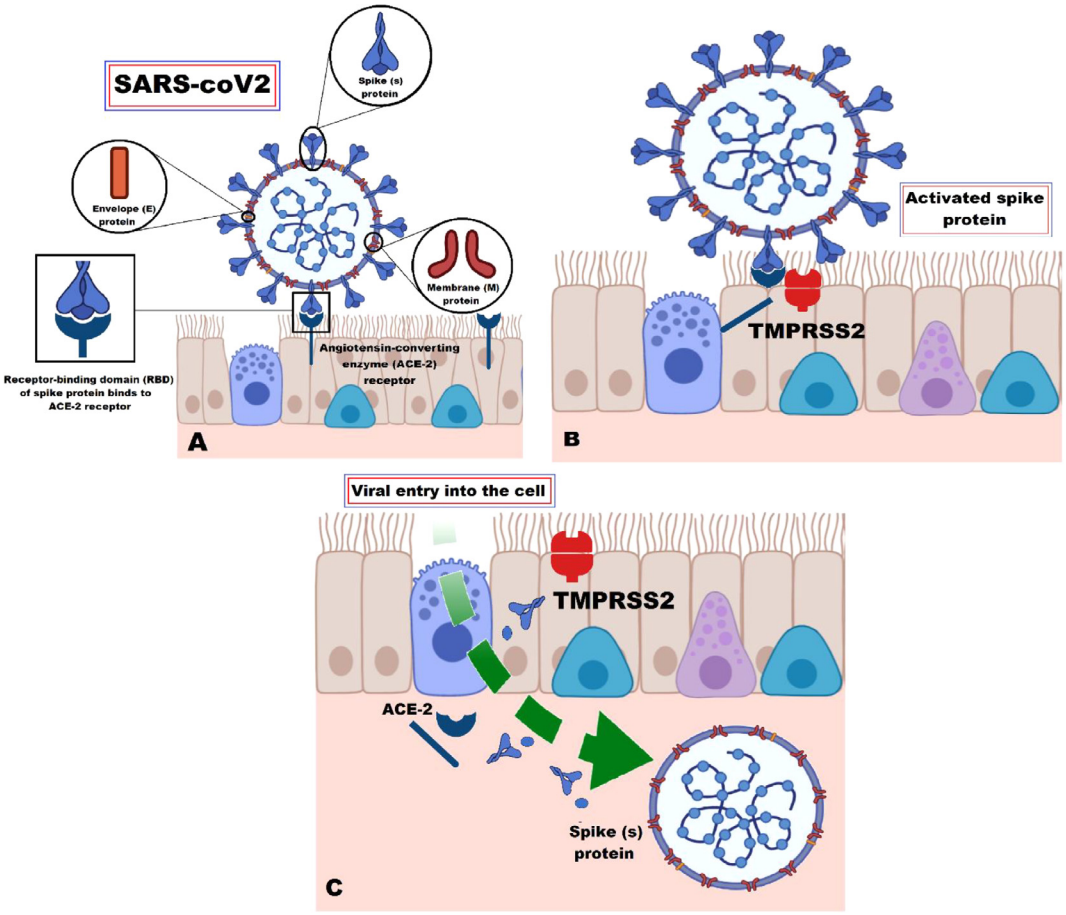

Fig. 1. A schematic representation of COVID-19 virus structure and disease pathophysiology. SARS-CoV-2 virus is one of coronaviruses that is covered with crown like projections called spike (S) glycoproteins and other three structural proteins; namely envelope (E), nucleocapsid (N) and membrane (M) proteins. SARS-CoV-2 can start infection by **(A)** binding S proteins functional subunits to the angiotensin converting enzyme-2 receptors on host cell surface; **(B)** activating transmembrane protease serine 2; followed by **(C)** cleavage of virus's S1 subunits from its S2 subunits and so, of the angiotensin converting enzyme-2 receptors; facilitating the virus-cell fusion. **ACE-2** = Angiotensin converting enzyme-2; **SARS-CoV-2** = Severe acute respiratory syndrome coronavirus-2; **TMPRSS2** = Transmembrane protease serine 2.

well recognized that activating pulmonary RAS can influence the pathogenesis of lung injury in different lung diseases such as pulmonary hypertension, acute respiratory distress syndrome (ARDS), asthma and pulmonary fibrosis [54]. As a consequence, pulmonary RAS has been described to participate in disease process or play a protective role against tissue injury [57] and thus, modulating RAS in the lung can successfully play a good role in the treatment of inflammatory lung disease [52,58].

The functional steps of RAS was firstly initiated by hepatic synthesis of a plasma globulin called renin substrate (or angiotensinogen) which could be enzymatically converted through renin secreted by juxtaglomerular cells of the kidney, into the biologically inactive decapeptide, namely angiotensin (Ang) I [59]. Subsequently, RAS exhibits two main axes based on two distinct enzymes responsible for cleavage of Ang I into angiotensin (Ang) II or Ang 1–7 [51], Fig. 2.

First axis involves generation of Ang II as the main effector via the angiotensin converting enzyme (ACE) and named the classical vasopressor axis ACE/ Ang II/ Ang II type 1 receptor (AT1) [60]. For the second axis, angiotensin converting enzyme II (ACE-2) was identified as a depressor for RAS activation through producing Ang 1–7 [61]. Henceforth, this axis ACE-2/ Ang 1–7/ Mas-1 has become an important area of scientific research interest [62].

3.2. ACE/Ang II/AT-1 axis and COVID-19

The ACE/Ang II/AT-1 axis has been well documented to drive a set of deleterious reactions in the lung through generating Ang II, the principal effector of this classical axis, involved in RAS mediated vasoconstriction, sodium retention, fluid overload, inflammation and fibrosis [63,64]. In addition, ACE has been reported to evoke bradykinin and substance P degradation, two local pro-inflammatory and protussive peptides which can stimulate cough reflex and nitric oxide (NO) release [65,66].

Specifically, pulmonary vascular inflammation contributes to a phenomenon called ACE "shedding," in which endothelial surface-bound ACE is released into the interstitium resulting in significant increase in the level of Ang II [67], which explains the detection of higher Ang II level in COVID-19 patients than normal [68].

Several studies declared that Ang II could act through two distinct G protein-coupled receptors (GPCR) subtypes, angiotensin II receptor type 1 (AT1R) and type 2 (AT2R), that were found to be expressed in human lung tissue; proving the local generation of Ang II in lung [65,69].

The majority of actions evolved by Ang II could be mediated by AT1 receptor via enhancing many complex intracellular signaling pathways including MAPK/ERK, PLCb/IP3/diacylglycerol, tyrosine kinases, and NF-kB [70]. Activating AT1 receptor had been shown to further stimulate monocytes, macrophages and vascular smooth muscle cells to produce the proinflammatory cytokines such as TNF-α and IL-6 [71–73]. On the contrary, AT2 receptor was documented to have a number of counterregulatory interactions against lung tissue injury via inhibiting inflammation, and fibrosis [74,75].

In addition to the known Ang II effects on promoting

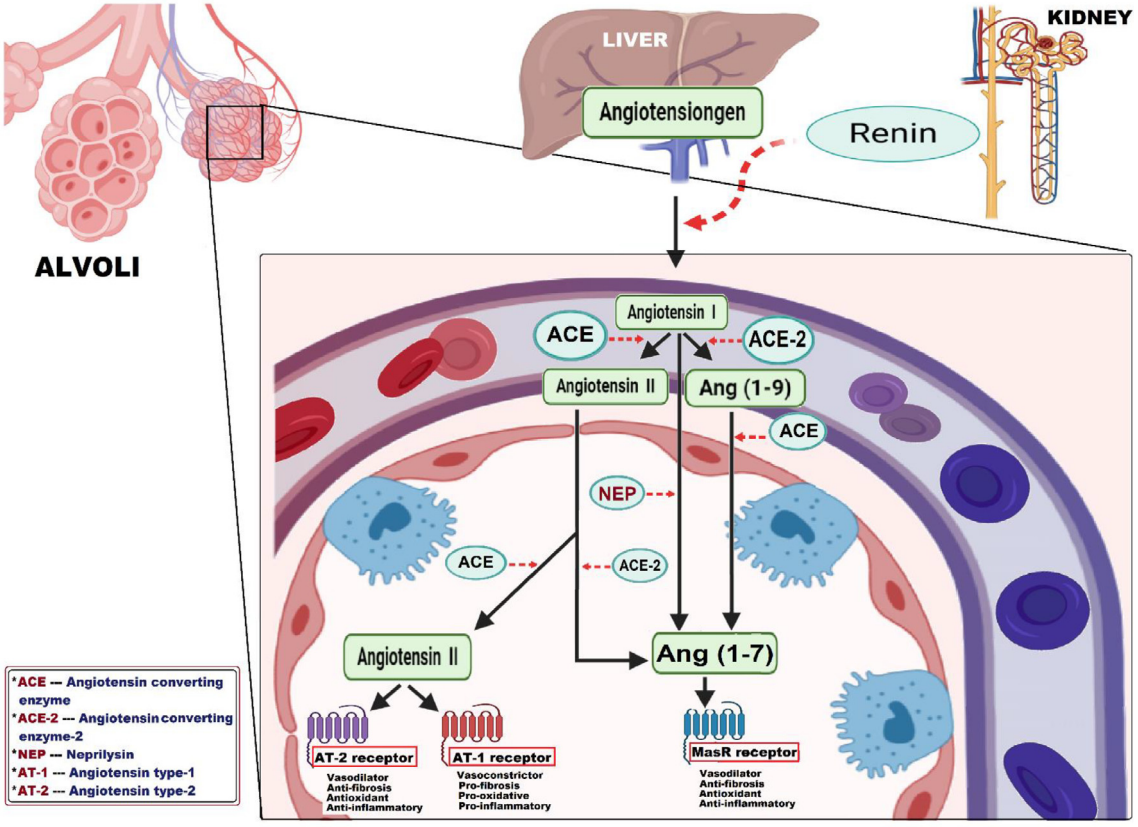

Fig. 2. A schematic diagram of pulmonary renin-angiotensin system (RAS) cascade. The pulmonary RAS cascade is initiated by converting angiotensinogen (synthesized in liver) through renin (secreted by juxtaglomerular cells of the kidney) into the biologically inactive angiotensin I. Based on angiotensin I degradation, RAS exhibits two main counterregulatory axes: the classical vasopressor arm; named ACE/ Ang II/ AT-1 axis, involves the conversion of angiotensin I by angiotensin converting enzyme into angiotensin II. Angiotensin II acts via angiotensin II type 1 receptor to induce vasoconstriction, fibrotic, oxidative and inflammatory reactions, which can be counteracted via stimulating angiotensin II type 2 receptor. The second depressor arm; named ACE-2 /Ang (1–7)/MasR axis, competes for hydrolyzing angiotensin I into angiotensin (1–9) by angiotensin converting enzyme-2 and then, into angiotensin (1–7) by angiotensin converting enzyme, in addition to neprilysin that directly produce angiotensin (1–7) from angiotensin I. To the same extent, angiotensin converting enzyme-2 can also degrade angiotensin II into angiotensin (1–7), that acts via MasR receptor to produce vasodilatation, anti-fibrotic, anti-oxidative and anti-inflammatory reactions. **ACE** = Angiotensin converting enzyme; **ACE-2** = Angiotensin converting enzyme-2; **Ang (1–9)** = Angiotensin (1–9); **Ang (1–7)** = Angiotensin (1–7); **AT-1** = Angiotensin II type 1 receptor; **AT-2** = Angiotensin II type 2 receptor; **NEP** = Neprilysin.

vasoconstriction, and pro-inflammatory cytokine release, there is also an increasing evidence that Ang II could induce vascular endothelial dysfunction [76,77], promoting the activation and aggregation of platelets and thereby, pro-thrombotic milieu [78].

Ang II could be associated with noticeable rise in the plasma level of endothelin-1 (ET-1) [79], which is a peptide secreted mainly from vascular endothelial cells (ECs), and basically works through the endothelin type A receptor (ET_A) in vascular smooth muscle cells and the endothelin type B receptor (ET_B) in ECs [80]. Consequently, ET-1 is described as the most potent bronchoconstrictor [81] and vasoconstrictor in the airways [82]. Practically, ET-1 acts as a key player of angiotensin II-induced endothelial dysfunction and platelets activation via inducing IL-6 release [83,84], which was documented to be correlated directly with the extent of endothelial dysfunction [85].

Endothelial dysfunction is generally characterized by an imbalance between endothelium-dependent relaxing and contracting factors, attributed to reduced production/availability of nitric oxide (NO); namely endothelium-derived relaxing factor (EDRF) [86,87]. NO acts as a potent endogenous vasodilator that could prevent platelet aggregation and leukocyte adhesion to ECs [88,89]. Since IL-6 would inactivate endothelial nitric oxide synthase (eNOS), it could disrupt NO production [90], decreasing its level and inducing a state of oxidative stress that may lead to Ang II-induced impairment in endothelial responses [91]

Postulating impaired endothelium functions as a principal factor in the pathogenesis of heart failure, hypertension and diabetes, it will be expected to classify the patients of such diseases as high risk groups for COVID-19 development [92–94].

Furthermore, platelets activation and aggregation may be noticed as a result of inflammatory reactions aggravated by endothelial dysfunction, leading to imbalance between coagulation and fibrinolysis [87]. It is clearly evident that continuing release of IL-6 can enhance hepatic thrombopoietin (TPO) mRNA expression resulting in thrombopoiesis stimulation and increase in circulatory platelets' numbers, known as (inflammatory thrombocytosis). Within this context, ET-1 can also mediate the synthesis of platelet activating factor (PAF), a potent phospholipid mediator of platelet activation and aggregation, that may activate platelets to stick together and aggregate. As a result, a platelet plug is formed as an initiator for blood clotting and intravascular thrombus formation [88,89], which is considered as a starting point for developing stroke [95].

Even though the high incidence of inflammatory thrombocytosis in COVID-19 patients, the laboratory results of severe cases showed the opposite; suffering from thrombocytopenia [23].The possible explanation is the depletion of both platelets and megakaryocytes as a result of multiple blood clots formed at the injured site, leading to less platelet production with more consumption as the disease severity increases [96].

Interestingly, endothelial dysfunction and platelet activation can successively together worsen the severity of COVID-19 infection. As known, both ET-1 and activated platelets, associated with endothelial dysfunction, [97] could promote leukocytes rolling, adherence to endothelium, activation and migration into the inflammatory sites, sharing in enhancement of leukocytes recruitment [98,99]. In addition, endothelial dysfunction can drive the fibrotic consequences following SARS-CoV-2 infection, developing pulmonary fibrosis as a result of releasing transforming growth factor- β1 (TGF-β1), the main fibrogenic cytokines implicated in pulmonary fibrosis, which could be induced by ET-1 action [100,101].

Taken into consideration the numerous harmful effects possibly induced by Ang II during COVID-19 pathogenesis, we found that most novel studies aim to use the anti-hypertensive drugs which act either by inhibiting the ACE activity or by blocking AT1 receptor, suggesting that action may mitigate the disease severity in COVID-19 patients.

On the other side, it has been proposed that enhancing the counter regulatory axis composed by ACE-2/Ang (1–7)/MasR axis may be the most helpful.

3.3. ACE-2/Ang (1–7)/MasR axis and COVID-19

ACE-2/Ang (1–7)/MasR axis, the depressor arm of RAS, was identified to mitigate the deleterious actions mediated by ACE/ Ang II/ AT1 [51]. Within this axis, ACE-2 competes with ACE by hydrolyzing Ang I into the nonapeptide angiotensin (Ang 1–9) which is further cleaved by the action of ACE into heptapeptide angiotensin (Ang 1–7), thus decreasing the amount of Ang I available for Ang II generation by ACE [102,103]. To the same extent, ACE-2 could also hydrolyze Ang II converting it into Ang (1–7) [104,105].

Until the year 2000, ACE has emerged as the key enzyme in the pulmonary RAS, but this was challenged by the discovery of its homologue; ACE-2 [106] which was found out to be broadly expressed in almost all types of lung cells, within the vascular endothelial and smooth muscle cells, types I and II alveolar epithelial cells and bronchial epithelial cells [107,108].

ACE-2 could negatively regulate the RAS in the lung through reducing Ang II/AT1 receptor signaling and activating the counter-regulatory Ang (1–7)/ Mas receptor pathway [54]. That finding was compatible with the animal studies showed that the use of RAS inhibitors could effectively relieve the symptoms of acute severe pneumonia and respiratory failure [109]. Consequently, the increased ACE-2 was addressed as a target for protection from predisposition to inflammatory lung diseases such as, acute respiratory distress syndrome (ARDS) [108,110].

Concerning COVID-19 pathogenesis, binding of SARS-CoV-2 to ACE-2 resulted in exhaustion of ACE-2, breaking the balance of the RAS system within the lung and then, exacerbation of pulmonary inflammatory reactions [109,111].

Being ACE-2 receptors widely expressed on vascular endothelial cells (EC) within the lungs [112], SARS-coV-2 can exploit them to induce and diffuse inflammatory cascades within endothelial cells disrupting their function; evidenced by the existence of viral elements and inflammatory cells within endothelial cells [113].

Thus, distributing ACE-2, as the main functional receptor for SARS-CoV-2, within human tissues will be the determinator for spreading of viral infection within the lung and other organs [108,114]. Both alveolar and bronchial membranes were reported to highly express ACE-2, which may explain the higher tendency of SARS-CoV-2 virus to harmfully affect lower airways than the upper ones [110,115]. However, recent reports indicate that few COVID-19 patients may also develop some signs and symptoms of upper respiratory tract infection (e.g. rhinorrhea, sneezing, or sore throat) [7,17,116].

Furthermore, it was reported that ACE-2 is also expressed in many epithelial cells of other organs than lung including kidney, blood vessels, intestine [110] and brain [117]. The fact which may explain the existence of some extra-pulmonary co-morbidities as myocardial dysfunction [30] and acute kidney injury (AKI) [118], gastrointestinal manifestations (diarrhea, vomiting or abdominal pain) [119], neurologic manifestations (altered mental status or seizures) [120,121].

Therefore, increased ACE-2 may be useless by promoting viral entry into lung cells, potentiating its devastating effect and enhancing mortality [122]. Consistent with these findings, suggesting ACE-2 activators such as, Diminazene aceturate (DIZE) [65], 4-[2-(4-carbamimidoyl phenyl) imino hydrazinyl] benzene carboximidamide and Xanthenone (XNT) [54] for counteracting COVID-19 pathogenesis will be in vain.

As a consequence, in order to diminish SARS-CoV-2 entry and its subsequent lung injury, pulmonary ACE-2 activity should be reduced. However, at the same time, reduced ACE-2 activity may contribute to worsening of the lung inflammation, by unopposed angiotensin II accumulation [31] and forcing the RAS to continuously increase the expression of cytokines [123].

Simultaneously, a previous data indicated that the decrease in the ACE-2 activity in a rat model of ARDS was paralleled by low amounts of Ang-(1–7) [124], which has been reported to play a beneficial role against pulmonary inflammation and fibrosis [125,126]. In this context, another study stated that treatment with protease-resistant, a cyclic form of Ang (1–7) (cAng 1–7), could restore the ACE-2 activity; attenuated the inflammatory response; decreased lung injury and improved lung function [124,127]. That confirms the positive relationship between Ang 1–7 and preserving the depressor role of ACE-2/Ang (1–7)/ MasR axis in pulmonary RAS. Hence, these data will attract the attention to the pivotal role of Ang (1–7) in COVID-19 pathophysiology and therapy.

3.4. Ang (1–7) and COVID-19

Ang (1–7) is a biologically active metabolite of the RAS that had become a peptide of interest in the last decade, because of its effective role in activating a number of crucial events for the homeostasis of normal physiological functions [128]. It was reported that Ang (1–7) could exert various effects, which are greatly in opposition to those of AT-1 receptor activation such as vasodilator, anti-inflammatory, anti-hypertrophy, anti-proliferative, anti-fibrosis and antioxidant effects [54,129].

Clinical and epidemiological studies have revealed the existence of a powerful link between the vasodilator effect of Ang 1–7 and its higher plasma levels in females; making them less liability to hypertension than males [130,131]. Several mechanisms have been attributed to Ang 1–7 in lowering blood pressure which can be explained as follows (i) Triggering eNOS to stimulate the release of NO, which could play a critical role in promoting the relaxation of blood vessels and inhibiting the platelet aggregation [132,133] (ii) Inducing natriuresis/diuresis [134], and (iii) Activating peroxisome proliferator activator receptors (PPARs), which in turn supports the availability of NO [135].

Interestingly, Ang 1–7 was documented to directly blunt the activation of pro-inflammatory signaling pathways induced by the Ang II-associated phosphorylation of MAPKs and NF-kB signaling [136,137], suggesting also the anti-hypertrophic effects of Ang 1–7 through normalization of MAPKs activity [130]. Moreover, Ang (1–7), by counteracting the Ang II effects, could also preserve the endothelial function through increasing nitric oxide bioavailability and inhibiting oxidative stress [138].

Taken together, Ang 1–7 could also reduce lung injury by suppressing the expression of fibrogenic molecules such as TGF-β1[139], which acts as a key mediator involved in pulmonary fibrosis [140].

Moreover, several researches have pointed out the antioxidant role of Ang 1–7 [54,130] that might be established by; (i) limiting the activation of NADPH oxidase, which is a membrane-bound enzyme complex involved in triggering ROS production through generating superoxide radicals [141], and/or (ii) normalizing the expression of antioxidant enzymes such as catalase and heme oxygenase-1 (HO-1)

Table 1
Main evidence about the several pharmacological mechanisms of NEP.

	Drug action	Drug name	Disease	Population	Main effects	References
Neprilysin (neutral endopeptidase; NEP)	Inhibitors	Racecadotril (acetorphan)	Acute Secretory Diarrhea	Rats, children and adult patients	Reduced the water and electrolytes hypersecretion into intestinal lumen by inhibiting the degradation of endogenous enkephalins in the intestinal epithelium	[181,272,273]
		Sacubitril/ Valsartan (Entresto)	Congestive heart failure (CHF)	Rats and CHF patients	Sacubitril elevates the NPs level, increasing sodium and water excretion in urine, dilating blood vessels, and reducing preload and ventricular remodeling	[182,274–276]
		Omapatrilat	Hypertension	Rats and hypertensive patients	Inhibiting the degradation of vasoactive peptides, including NPs and BKs, causing blood vessel dilation and reduction in ECF volume	[277–280]
		Sacubitril	Diabetes	Mice, rats and diabetic patients	Demonstrated to regulate glucose metabolism by improving glycemia and reducing time to initiation of insulin therapy	[185,281,282]
	Agonists	Recombinant soluble sNEP	Alzheimer's disease (AD)	Mice and hippocampal cells HT22	Reduced the amyloid-beta accumulation and improved memory impairment	[190,283]
		Recombinant neutral endopeptidase (EC 3.4.24.11)	Ulcerative colitis	Mice	Inactivated the expression of proinflammatory neuropeptide Substance P and the adhesion molecule ICAM-1	[284,285]
		Recombinant neutral endopeptidase (EC 3.4.24.11)	Lung cancer	Lung cancer cell lines and mice	Degrading the biologically active peptides implicated in the stimulation of lung cancer; inhibiting lung cancer cell growth	[286]
		Recombinant human neutral endopeptidase (rhNEP)	Pancreatic elastase-induced lung injury	Mice	Degraded the proinflammatory mediators (chemokines, endothelin, bradykinin) involved in neutrophil sequestration.	[287]
		Recombinant neutral endopeptidase (EC 3.4.24.11)	Tachykinins -induced cough and dyspnea	Guinea pigs	Inhibiting substance P-induced cough is suggested by high affinity of substance P and other tachykinins to neutral endopeptidase	[288,289]

BKs = Bradykinins; **ECF** = Extracellular fluid; **ICAM-1** = Intercellular adhesion molecule-1; **NPs** = Natriuretic peptides.

[130], as well as the nuclear factor erythroid 2–related factor 2 (Nrf2), that acts as an emerging regulator of cellular resistance to oxidants [142].

Other observation and experimental evidence suggested that endogenous ACEIs effects of Ang (1–7) can be mediated by its unique membrane bound G protein-coupled receptor known as Mas (MasR) [143], which was revealed to be found in the thin areas of the bronchial epithelium and smooth muscle [144]. MasR could direct the Ang 1–7 biological responses via the MasR/cAMP/protein kinase A (PKA) signaling [145], which was previously validated by administrating AVE 0991 (a nonpeptide mimetic of Ang 1–7 as a specific ligand (agonist) for MasR [130].

Subsequently, attention should be drawn to specifically trigger the Ang (1–7) as a potential therapeutic agent able to mitigate the lung injury in patients with COVID-19 infection, without increasing ACE-2 activity.

There are different formulations of Ang 1–7 are being developed e.g. AVE-0991 [146], HPβCD/Ang 1–7 [147], CGEN-856 [148], NorLeu3-A [149] and cyclic Ang 1–7 [150] and used to demonstrate its therapeutic potential in numerous animal models of human diseases, including hypertension, heart failure, stroke, diabetes mellitus, atherosclerosis, renal disease and pulmonary arterial hypertension [130,145,151]. However, therapeutic attempts and clinical trials are still underway because of Ang (1–7) rapid in vivo degradation by ACE [130].

On the other hand, previous studies emphasized that Ang (1–7) could induce vasodilatation in rats of Mas-deficient vessels [152] and in rats pretreated with A779 (MasR blocker) [153]. The former observed data suggested that Ang (1–7) might also interact with an additional specific receptor other than MasR to elicit vasodilatation [154]. Indeed, Ang (1–7) have been shown to stimulate also the bradykinin (BKs) pathway via preventing the BK hydrolysis [155].

BKs are one of the formed kinins that can play significant roles in regulating tissue injury, inflammatory responses and vascular permeability [156]. They have a little direct impact on the activation and recruitment of inflammatory cells, but they could work indirectly through stimulating the airway epithelial cells and lung fibroblasts through producing a wide array of cytokines, including IL-6, IL-1, IL-8, granulocyte colony stimulating factor (G-CSF), GM-CSF and macrophage chemoattractant protein-1 (MCP-1) [157158–160]. BK action was mediated by G-coupled receptors, namely BK receptor (BR) [156] that amazingly found to be interacted with the Mas receptors in order to regulate the vasodilator effect of the Ang (1–7) [161].

At the same time, it was found that the reduction in ACE-2 mRNA expression within the lungs of STZ diabetic rats was linked with an increase in circulating Ang II, but without any significant change in the production of Ang (1–7) [162,163], ensuring that pulmonary ACE-2 was not the only enzyme responsible for Ang (1–7) production, but there might be another enzyme contributing to its synthesis.

By the time, the classical view of RAS has been further expanded and become well established than previously conceived. As a consequence, it was discovered that there was another alternative pathway by which Ang (1–7) is produced, instead of that based on ACE-2. That way was disclosed to degrade Ang I directly into Ang (1–7) by another RAS member, called NEP.

3.5. NEP and COVID-19

NEP (neutral endopeptidase or neprilysin, previously known as CD10) is a member of transmembrane zink-metalloendopeptidase that particularly highly expressed in both kidney and lung [164–166]. NEP was also found in a number of other tissues, as epithelia of breast, prostate, stomach and in the central nervous system [167–169]. NEP had been also shown to be present in a soluble circulating form (cNEP) within several body fluids including urine, cerebrospinal fluid and plasma [170].

Although NEP can discriminately hydrolyze a broad spectrum of

physiologically relevant substrates, it was found to possess an obvious substrate specificity. Classically, NEP exhibits a size-related specificity that enables it to hydrolyze only peptides with a small molecular weight generally at or below 3,000 Dalton [171]. As well, NEP has been also described to show a distinction between substrates being cleaved 'in vitro' and that being cleaved 'in vivo'. Initially, NEP was reported to specifically cleave more than 7 peptides 'in vivo' including natriuretic peptides (NPs) (Atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and B-type natriuretic peptide (BNP)), BKs, neuropeptides (substance P, enkephalins), Gastrin, Chemotactic peptide formyl-Met-Leu-Phe (fMLP), versus 26 peptides 'in vitro' such as IL-lβ, Oxytocin, Gastrin-releasing peptide (GRP), ET-1, Ang I and II……etc [172–174]. By time, more substrates had been proposed with varying levels of 'in vitro' and/or 'in vivo' proof of cleavage. Among that, GRP, ET-1, Ang I which have been proved to be additionally metabolized 'in vivo' by NEP [162,175,176], emerging the evidence that NEP could play an important role in many physiological and pathological conditions [177], Table 1.

For CVS patients, NPs were known to be of therapeutic importance in lowering blood volume by inducing natriuresis, in which excess sodium can be excreted in urine with accompanying water by the renal tubules [35]. Previous clinitcal trials proved that administering synthetic NPs might be associated with some limitations especially on the long run [178,179], that pushed them to depend on using Neprilysin inhibitors (NEPi) such as (thiorphan or candoxatrilat) to prolong and potentiate the beneficial effects of vasoactive/NPs via inhibiting endogenous NPs degradation [180].

NEPi have been used for decades to treat acute diarrhea [181]. However, they are now developed and emerged as a pharmaceutical target for different CVS diseases. NEPi have been used mainly in people with congestive heart failure and a reduced left ventricular ejection fraction (LVEF) [182]. However, using NEPi (e.g. candoxatril) solely for hypertension treatment was ineffective, because NEPi could inhibit Ang II degradation, increasing its associated simultaneous detrimental effects. Therefore, combining NEPi either with ACEi (e.g. omapatrilat) or ARBs (e.g. LCZ696) become a necessity to overcome this limitation [183,184].

Another critical aspect for the pharmacological role of NEPi was achieved in treating diabetes via inhibiting the breakdown of some substrates known to modulate glucose metabolism, such as incretin glucagon-like peptide-1 (GLP-1), NPs and BKs [185].

Within the brain, NEP had also proved to hold a great beneficial role in the neurological disorders such as Alzheimer's disease (AD) on both in vitro and in vivo studies [186–188]. Multiple lines of evidence highlighted the presence of many amyloid plaques in the form of β-amyloid (Aβ) peptide in the brains of AD patients with dementia [189]. It was worthy mentioned that NEP was one of the major Aβ peptide-degrading enzymes in the brain, whose expression was documented to be lower in the brain of AD patients [190] supporting the role that NEP can play in the prevention and treatment of AD.

In addition to the above mentioned, NEP seems to play a protective role in the pathogenesis of lung injury since significant decrease in the NEP enzymatic activity in the lung of mice with ALI was associated with inactivation of the tachykinins degradation pathway and consequently, reducing uncontrolled inflammation in ALI/ARDS and in other neurogenic respiratory diseases [37,191,192].

Lung inflammation could induce hyperplasia in the pulmonary neuroendocrine cells (PNECs) of both respiratory bronchioles and alveoli [193,194], resulting in excessive production of GRP [195].

GRP was known to be one of the Bombesin-like peptides that can be expressed and released by PNECs into the surrounding airway parenchyma in response to various stimuli like hypoxia or irritation [196,197] to regulate the neutrophil chemotaxis and macrophage infiltration within the lung tissue [198,199]. GRP could act via stimulating Gastrin-releasing peptide receptor (GRPR) at the surface of macrophages, which in turn, would enhance the release of early inflammatory mediators contributing to the recruitment of neutrophils [200,201].

More neutrophil infiltration within the lung is usually associated with high tendency for lung tissue damage [202,203], since they would be involved in breakdown of basement membrane integrity within the bronchiolar/alveolar architecture and thereby, diminution of pulmonary function. Moreover, during the deleterious inflammatory reactions, as in pneumonia, neutrophil lifespan is prolonged to generate more superoxide radicals resulting in damage of the surrounding normal tissue [204].

Interestingly, NEP can play a vital role during lung inflammation through its catabolic effect on (GRP) [205] in addition to its presence on the plasma membrane of neutrophils modulating their chemotactic responsiveness via cleaving the chemotactic peptide formyl-Met-Leu-Phe (fMLP) which resembles an effective chemotactic agonist in response to GRP [206,207]. Thus, breaking both GRB and fMLP peptide by NEP will cut the way for recruiting more neutrophils into site of injury and consequently, grab the reins.

On the other hand, once neutrophils being activated at inflammatory sites, they could secrete high concentration of several serine proteases into the extracellular environment to degrade host pathogens, recruit more cytokines and stimulate further tissue damage [208,209]. Cathepsin G was reported to be one of the neutrophil-derived serine proteases that is abundantly found in the azurophil granules and known to degrade both Angiotensinogen and Ang I into Ang II [209,210].

So far, NEP can additionally take a part in decreasing the pro-inflammatory, oxidative and pro-fibrotic effects of Ang II by minimizing the release of cathepsin G and consequently, its action on Ang I [211–213].

As NEP was reported to have more catalytic activity than ACE-2 in cleaving Ang I into Ang (1–7), it could also effectively enhance the protective activities associated with Ang (1–7) in the lung [214]. As well, NEP could not affect lung Ang (1–7) metabolism because it was involved in the metabolism of Ang (1–7) within tissues other than pulmonary tissues, as renal cortex. On the other hand, ACE was recorded to be the major enzyme responsible for Ang (1–7) metabolism in the pulmonary membranes by hydrolyzing it to Ang (1–5), and then, into Ang (3–5) by the action of aminopeptidases [215]. Besides, NEP shows higher activity than ACE towards BKs degradation, resulting in inhibition of the bradykinin-induced inflammatory cells influx [125,216].

Despite multiple data confirming the expected role of NEP in relieving the pulmonary inflammatory response, its effect on reducing exacerbation of acute severe pneumonia in COVID 19 patients has not been highlighted yet.

Hence, the question now, may the reviewed actions of NEP pathways be sufficient to impose a new effective strategy for COVID-19 management as compared to the suggested repurposed drugs?

4. Main repurposed drugs for COVID-19

World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) guidelines only provide supportive care. However, many drugs repurposed based on host response in order to defeat COVID-19, Table 2 [217].

4.1. Anti-inflammatory agents

Recently, there is an empirical use of anti-inflammation therapy in critical patients of COVID-19 presented with severe complications in order to prevent further injury and suppress Cytokine storm manifestations as ARDS and other organs damage till even death. Main anti-inflammatory medications include, non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, chloroquine and statins [22].

Numerous observational data support a strong association between

Table 2
Main repurposed drugs for COVID-19.

Classes of drug used	Main member (s)	Main molecular mechanisms of action	Use Limitations	References
Anti-inflammatory agents	Non-steroidal anti-inflammatory drugs (NSIDs) ● Ibuprofen ● Diclofenac	Inhibit cyclooxygenase enzymes (COX-1/COX-2) that mediate the bioconversion of arachidonic acid into prostaglandins (PGs) which, in turn, control inflammation	Increased risk of stroke and myocardial infarction in acute respiratory tract infections, induced nephrotoxicity in susceptible covid-19 patient groups which is exacerbated by fever and dehydration.	[219–221]
	Corticosteroids ● Prednisolone	Modulate a variety of the inflammatory cytokines (including IL-1, IL-6, IL-8, IL-12 and TNFα), reduce IFN-γ- (IP-10) and MCP-1, potent mediators of the immune inflammatory response	Inhibit synthesis of anti-inflammatory molecules as lipoxins and resolvins, delaying resolution of inflammation with increase susceptibility for secondary infection, stimulation of hypothalamic-pituitary adrenal axis can also induce lymphocytopenia	[24,219,260,261]
	Specific anti-cytokines ● Anakinra ● Tocilizumab	Anakinra is IL-1 receptor antagonist and tocilizumab is IL-6 inhibitor, reducing virally driven hyperinflammation	Anakinra increases risk of infection, mainly pneumonia, induce neutropenia since IL-1 is a neutrophil attractant and growth factor and Tocilizumab reduces CRP levels, masking the clinical symptoms	[10,22,262]
	Anti-inflammatory cytokines ● IL-37 ● IL-38	Suppress inflammatory activity via IL-1 inhibition that produces other proinflammatory cytokines	Inhibition of gamma-interferon production resulting in more viral burden and early dissemination of viral infections	[17,263]
	Chloroquine (CQ) & Hydroxychloroquine (HCQ)	Anti-inflammatory actions by reducing production of the inflammatory cytokines, might interfere with ACE2 receptor glycosylation, thus preventing SARS-CoV-2 binding to target cells and immunomodulatory benefits by affecting cell signaling in viral infections	Its poisoning has been favored with possible life threatening arrythmias in cardiac patients, retinal toxicity has been described with long term administration of CQ and HCQ, may precipitate liver & renal impairment in susceptible patients	[217,227,264,265]
Estrogens	Estrogens ● Estradiol (E2) Selective estrogen receptor modulators (SERMs) ● Toremifene	Could suppress TMPRSS2 expression in the lung which is essential for SARS-CoV-2 entry, increase Ang-(1–7) production through ER-α-mediated stimulation of ACE1 and ACE2 expression and activity	Male sexual functions regarding erection, spermatogenesis and libido are adversely affected by estrogen exposure, long-term therapy may precipitate hypertension, cerebrovascular stroke and thromboembolism, increased risk of cervical and breast cancer in high risk patients	[235,237,238,266,267]
Renin-angiotensin system (RAS) blockers	ACE inhibitors ● Captopril Angiotensin II type 1 receptor blockers (ARBs) ● Valsartan	Enhancing the ACE-2/ Ang-(1–7)/ Mas axis to increase the production of ang (1–7) which, in turn, can counteract the activity of ACE/ Ang II/ AT1R axis, ARBs may preserve ACE-2 in competition with SARS-CoV-2 entry into the cell	ACE inhibition suppress kininase-II, which may be followed by accumulation of the protrusive mediators (bradykinin and substance P) in the upper respiratory tract or lungs resulting in dry cough and angioedema in susceptible individuals, ARBs may show upregulation in the membrane bound ACE-2 facilitating the coronavirus entry and worsen then its course	[240,241,268,269]
	Direct renin inhibitors (DRI) ● Aliskiren	Competitive inhibition of renin, lower the formation of Ang I, and therefore of Ang II and Ang (1–7) reduction in ACE2 expression	Same adverse effects as other RAS blockers mainly cough, contraindicated in old patients with renal or hepatic impairment	[28,270,271]

ACE = Renin Angiotensin System; **ACE-1** = Angiotensin Converting Enzyme 1; **ACE-2** = Angiotensin Converting Enzyme 2; **Ang-(1–7)** = Angiotensin 1–7; **COX-1** = Cyclooxygenase-1; **COX-2** = Cyclooxygenase-2; **CRP** = C-reactive protein; **ER-α** = Estrogen receptors alpha; **IFN-γ- (IP-10)** = Interferon gamma-Induced Protein 10; **IL** = Interleukin; **MCP-1** = Monocyte chemoattractant protein 1; **TMPRSS2** = Transmembrane Protease Serine 2; **TNFα** = Tumor Necrosis Factor Alpha.

use of **NSAIDs** in management of lower respiratory tract infections and higher incidence of complications including fulminating pneumonia, pleural effusions and dissemination of infection [218]. NSAIDs may also induce nephrotoxicity among susceptible covid-19 patient groups and is exacerbated by fever and dehydration [219]. Consequently, some studies recommend avoiding use of NSAIDs e.g. ibuprofen and diclofenac as the first choice for fever control and pain symptoms in COVID-19 infection and using paracetamol instead [220,221].

Previous study demonstrated that **corticosteroids**-treated asthmatic patients showed enhanced NEP expression in their airway epithelium as compared to nonsteroid-treated ones. This fits the hypothesis that the anti-inflammatory effect of corticosteroids within the airways may be partially mediated by upregulating NEP [222].

Despite of possible benefits gained from the anti-inflammatory effect of corticosteroids, they will be associated with serious impairment in the immune system of severe COVID-19 cases [22]. Corticosteroids may delay the viral elimination and increase susceptibility for the secondary infection resulting in deterioration of the disease especially with immune system impairment [223]. Other side effects associated with corticosteroid treatment include hyperglycemia, central obesity and hypertension which represent an obstacle against their use in people at higher risk for COVID-19 especially diabetic, cardiac and hypertensive patients [217].

Auyeung et al., 2005 reported that there is no survival benefit for treatment of SARS patients with corticosteroids [224]. Another study on corticosteroid therapy of MERS patients has revealed no mortality difference with delayed clearance of MERS-CoV from lower respiratory tract [225]. Moreover, there is no evidence from any clinical trials supporting its administration for COVID-19 [22].

In order to overcome the immune suppression induced by corticosteroids, a variety of other therapies have been developed to act directly as specific anti-cytokines (e.g. anakinra or tocilizumab) [10] or anti-inflammatory cytokines (e.g. IL-37 or IL-38) [17] without targeting the immune system and have proven to be effective in treating several syndromes that triggered by cytokine storm [123].

According to previous studies, **Chloroquine (CQ)** and its less toxic metabolite, hydroxychloroquine (HCQ) possess anti-inflammatory and immunomodulatory benefits by affecting cell signaling in viral infections. CQ/HCQ also exhibit a wide variety of antiviral reactions against several viruses including members of the flaviviruses, retroviruses, and coronaviruses [25].

CQ and HCQ can prevent the attachment of viral particles to their cell surface receptor, modulate pH in order to inhibit pH-dependent steps of viral replication or interfere with post-translational modifications (PTMs) of viral proteins [217,226].

An enough pre-clinical evidence considering CQ effectiveness for treatment of COVID-19 showed reduction in the pneumonia exacerbation, improving lung imaging findings and high rate of virus nucleic acid test negativity. Accordingly, CQ phosphate in Guidelines (version 6) for treatment of COVID-19 has been recommended with oral administration twice daily at a dose of 500 mg (300 mg for chloroquine) for adults and no more than 10 days [22].

However, there is a narrow margin between CQ/HCQ therapeutic and toxic dose. Its poisoning has been favored and life-threatening in patients with cardiac disorders [227]. It is also contraindicated for people with retinopathy, elevated liver enzymes, heart rhythm disorders (as QT prolongation) or allergy to CQ/HCQ [228]. Further, efficiency and safety of CQ/HCQ for COVID-19 is still unclear and needs a confirmation depending on more preclinical and clinical trials [229].

Statins are the widely used cholesterol lowering drugs, that were also reported to improve endothelial functions via lipid-independent mechanisms; mediated by their anti-inflammatory and anti-oxidant properties as well as their ability to restore vascular NO bioavailability [230]. Because of their immunomodulatory effect, they have also proven to be beneficial as adjuvant therapy in patients with different auto-immune inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis) [231]. As a consequence, some hospitals included statins in the treatment protocol of COVID-19. Although statin therapy is usually well tolerated, their use in COVID-19 patients may increase the incidence and severity of myopathies and acute kidney injury [232]. Moreover, statin drugs may increase IL-18 levels which can promote severe pneumonia, deteriorating SARS-CoV-2–induced ARDS and mortality, especially in elderly patients who are more likely to use these drugs [233].

4.2. Estrogens and selective estrogen receptor modulators (SERMs)

Sex differences in health outcomes following COVID-19 may be attributed to sex-dependent production of steroid hormones. Estrogen has been reported to attenuate inflammation which might protect women compared to men [234]. Estrogen signaling are also known to downregulate MCP-1 expression and promote adaptive T cell response by stimulating neutrophil recruitment [235].

It has been also reported that SERMs, like Toremifene, exhibits potential effects in blocking various viral infections as SARSCoV and MERSCoV virus [236] through interacting with and destabilizing the virus membrane glycoprotein resulting in inhibition of its replication [237].

Wang et al., 2020 suggests that treatment with estrogens and estrogen-related compounds as estradiol (E2) could suppress the expression of TMPRSS2 in the lung resulting in decreased mortality to SARS-CoV infection [235].

An estrogen receptors/RAS interaction has been demonstrated in several studies. E2 was detected to drive RAS to increase Ang-(1–7) production through estrogen receptor (ER α) mediated stimulation of ACE1 and ACE2 mRNA expression and activity. A sex difference has been revealed in the expression of RAS components [238].

4.3. Renin-angiotensin system (RAS) blockers

There is a controversy about the role of RAS blockers including, ACE inhibitors and/or angiotensin II type 1 receptor blockers (ARBs) in treating COVID-19 and their exact roles still remain unclear [28,32,239].

Their use has been suggested to be of a value through increasing ACE-2 that may have a protective effect against virus-induced lung injury by preserving ACE-2 in competition with SARS-CoV-2 entry into the cells [28]. Another mechanism by which ACE-2 can prevent lung damage and attenuate the pulmonary fibrosis, will be via enhancing the ACE-2/Ang-(1–7)/Mas axis to increase the production of ang (1–7), which in turn can counteract the activity of the ACE/AngII/AT1R axis [137].

On the other hand, it was known that ACE inhibitors could block the breakdown of bradykinin increasing its level and then, promoting its associated inflammatory reactions resulting in more deterioration in the health state [240]. Additionally, it has been expected that patients receiving ARBs may show upregulation in the membrane bound ACE-2 facilitating the coronavirus entry and worsen then its course [241].

The suggested explanation may be attributed to the increase in angiotensin II level that probably pushes it to act as an increased substrate loaded on the ACE enzyme, resulting in shifting a part of Ang II to be converted by the action of ACE2 into Ang (1–7), that may be associated with ACE-2 upregulation [32].

Other agents acting on the RAS, such as beta-blockers and direct renin inhibitors (DRI) to lower AngI formation and thereby, AngII and Ang (1–7). However, till now, no one discussed their impact on the severity and prognosis of COVID-19 [28].

On the contrary, lacking Ang (1–7) will be of negative effect on lung health. So, there is an urgent need to suppose a pathway that can ensure the increase of Ang (1–7) level without upregulating ACE-2. That effect may be attained by keeping ACE activity to enhance the pulmonary metabolism of Ang (1–7) and at the same time, shifting the RAS system

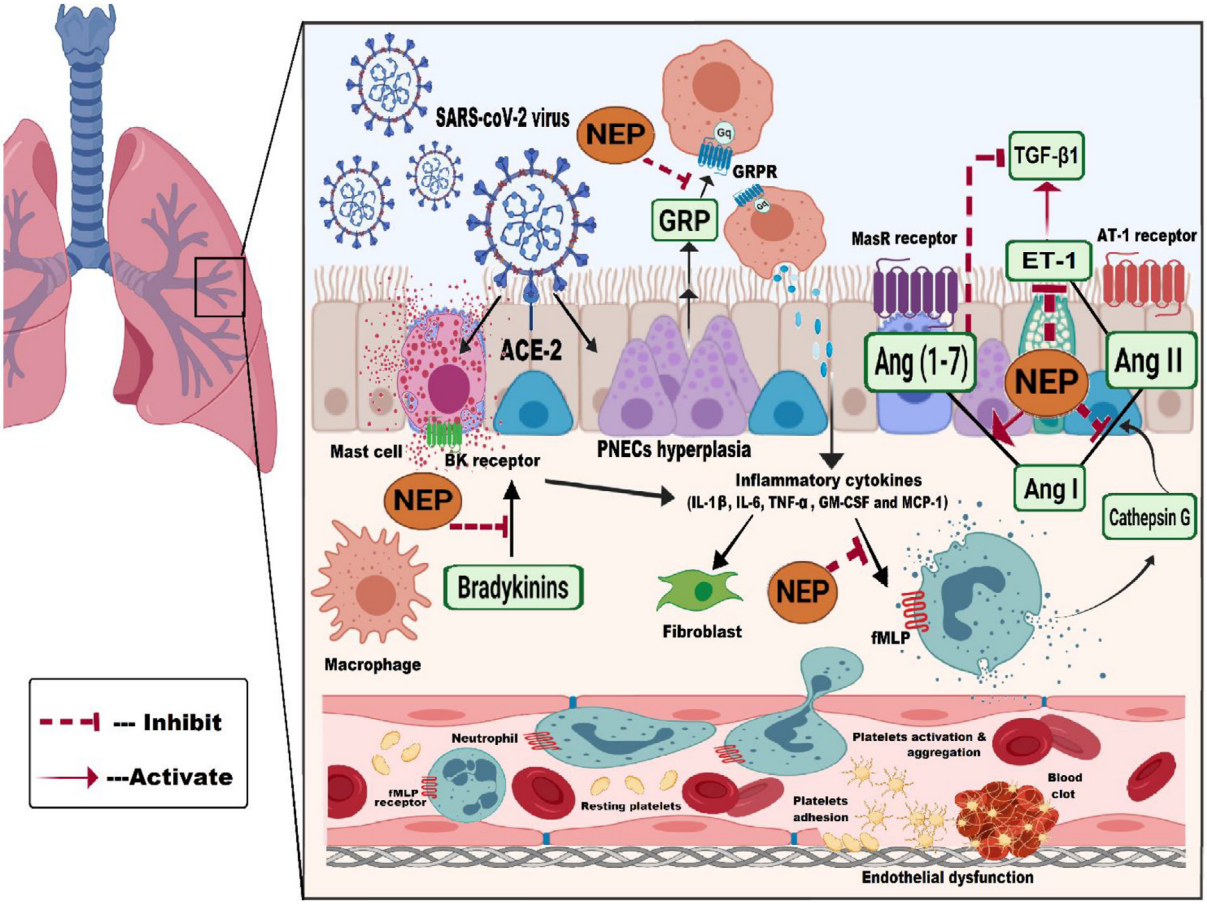

Fig. 3. A schematic diagram showing the NEP-dependent therapeutic strategy for COVID-19. Following binding of SARS-coV-2 virus to ACE-2 receptor on the cell membrane surface, lung may show pulmonary neuroendocrine cells hyperplasia with infiltration of several inflammatory cells. The hyperplasia may produce excessive Gastrin-releasing peptide into the surrounding airway parenchyma to stimulate Gastrin-releasing peptide receptor on the surface of macrophages, which in turn, will enhance release of inflammatory mediators such as (IL-1β, IL-6, TNF-α, GM-CSF and MCP-1) contributing to neutrophils recruitment. Neprilysin may degrade the produced gastrin-releasing peptide inhibiting subsequent release of inflammatory cytokines. At the same time, neprilysin may also cleave the chemotactic peptide Formyl Methionyl-Leucyl-Proline; by which neutrophils are efficiently migrated; altering their chemotactic responsiveness and recruitment. NEP may withstand the potent cytokine storm, through :(i) minimizing Angiotensin II via preventing the proteolytic cleavage of angiotensinogen and Angiotensin I into Angiotensin II by neutrophil-derived Cathepsin G and via regenerating the synthesis of endogenous Angiotensin (1–7) that by itself may protect against pulmonary fibrosis through reducing TGF-β1 expression, (ii) breaking bradykinins, blocking its action on its receptors on mast cell, inhibiting release of inflammatory cells and thereby, fibroblasts activation that may participate in the development of lung fibrosis, (iii) degrading endothelin-1 and consequently, inhibiting TGF-β1 release and (iv) stabilizing Ang II-induced endothelial dysfunction as well as suppressing platelet activation and aggregation that initiate blood clot formation. **ACE-2** = Angiotensin-converting enzyme 2; **Ang I** = Angiotensin I; **Ang II** = Angiotensin II; **Ang (1–7)** = Angiotensin (1–7); **AT-1** = Angiotensin II type 1 receptor; **BKs** = Bradykinins; **ET-1** = Endothelin-1; **fMLP** = Formyl Methionyl-Leucyl-Proline; **GRP** = Gastrin-releasing peptide; **GRPR** = Gastrin-releasing peptide receptor; **MasR** = Mas receptor; **NEP** = Neprilysin; **PNECs** = Pulmonary neuroendocrine cells; **SARS-CoV-2** = Severe acute respiratory syndrome coronavirus-2.

away from ACE/Ang II/AT-1 axis to avoid its associated inflammatory and oxidative activities. We suggest that NEP may achieve this complicated equation.

5. NEP-dependent strategy for COVID-19 therapy

Based on previous literature that addressed several beneficial and protective effects displayed by NEP during lung injury, we postulate that increasing NEP activity may mitigate COVID-19 pathogenesis. Lung of COVID-19 patients showed pneumocyte hyperplasia with inflammatory cellular infiltration [242], confirming the release of excessive GRP into the surrounding airway parenchyma as a result of PNECs hyperplasia [193,194,196,197].

Considering the documented links between high GRP level and both neutrophil chemotaxis and infiltration as well as reduction in food and water intake [243], it is not surprising to detect high neutrophil count [244] and anorexia in severe COVID-19 patients [245].

Thus, we expect that GRP is the first spark in initiating neutrophils recruitment as well as cytokine storm, which are the main pillars in COVID-19 pathophysiology. Our suggested hypothesis herein depends on two main aspects, Fig. 3:

NEP may abrogate GRP-induced neutrophil chemotaxis via cleaving GRP and degrading fMLP peptide that can modulate the chemotactic responsiveness of neutrophils. On the other aspect, NEP may withstand the potent cytokine storm, which was prescribed to be one of causes for lung damage progression and death in COVID-19 patients.

We suggest that NEP can diminish the release of inflammatory cytokines that may increase sensitivity of target cells for further stimulation by SARA-CO-2 virus [246,247]. Thus, NEP can improve lung histopathology and enhance tissue survival through two mechanisms:

Firstly, interfering with Ang II formation via preventing the proteolytic cleavage of angiotensinogen and Ang I into Ang II by neutrophil-derived Cathepsin G [209–211] that is expected to be released continuously in response to uncontrolled neutrophil activation associated with COVID-19 patients and via regenerating the synthesis of endogenous Ang (1–7), expected to be minimized because of ACE-2 exhaustion by SARA-CO-2 virus [109]. Ang (1–7) by itself may protect against pulmonary fibrosis through reducing TGF-β1 expression [139].

Secondly, breaking BKs and thereby, inhibiting its role in activation and recruitment of the inflammatory cells.

However, recorded findings suggest that lung damage caused by COVID-19 is induced by an alternative mechanism rather than hyper-infammatory injury. It likely seems that endothelial activation and associated pulmonary intravascular coagulopathy are the contributing factors in COVID-19 pathogenesis [18].

Within this context, NEP may exert a critical role in suppressing ET-1 that mediates angiotensin II-induced endothelial and platelets dysfunction. Yet, NEP may minimize the chance for Ang II formation, which was reported to be a potent stimulator of ET-1 in endothelial cells [248]. Even, NEP can additionally degrades ET-1, preventing its associated inflammatory injury and eventual fibrotic cascade in the lung [81,175].

Furthermore, we speculate that NEP may be helpful in dealing with individuals at high risk groups for COVID-19 that exhibit many obstacles in their management. NEP may regulate blood pressure in cardiovascular and hypertensive patients indirectly via decreasing both blood and tissue levels of Ang II by: (i) increasing Ang I substrate availability a result of inhibiting cathepsin G-mediated neutrophil release, and (ii) augmenting the rate of Ang I conversion into Ang (1–7), that previously reported to exert a stimulatory effect on ANP secretion via MasR [249].

For diabetic patients, we demonstrate that NEP may regulate pancreatic RAS flux to improve glycemic conditions. In response to NEP-mediated degradation 'in vitro', NEP may evoke the insulin secretory ability of Ang (1–7) via hydrolyzing it into the biologically active Ang (1–2) dipeptide in pancreatic islets [33,250].

Numerous 'in vivo' and 'in vitro' experiments have been made to increase NEP expression. One study speculated that dexamethasone could enhance NEP expression in airway epithelial cells via promoting its transcription and synthesis [251]. Another prior finding demonstrated that Valproic acid could reduce plaque formation and improve learning deficits via up-regulating NEP in APP/PS1 transgenic mice [252]. Recently, serotonin and its derivatives were explored to ameliorate symptoms of AD induced in mouse via enhancing NEP up-regulation [253].

Several lines of evidence identified that hormones such as androgens [254] and estrogen [255] could also positively regulate NEP expression, suggesting that decline in levels of androgen or estrogen associated with aging would accompany by decrease in NEP synthesis, which may be an important factor for increasing the risk of COVID-19 infection among elderly.

On the other hand, several findings investigated the up-regulating effect of some natural products on NEP expression such as Apigenin, Luteolin, and Curcumin, (-)-Epigallocatechin-3-gallate as well as Resveratrol [256–258]. In China, Naoerkang (NEK), a traditional Chinese herbal medicine, improved the ability of learning and memory in rats model of AD by increasing NEP expression in their hippocampal tissues [259].

However, some scientists aimed to produce recombinant NEP (r NEP) instead, as Park et al., 2013 who prepared recombinant soluble NEP from insect cells to be intracerebrally injected into AD mice [238].

Therefore, we finally suggest that therapeutic strategies aimed to increase NEP expression and/or activity may be of great benefit for prevention and treatment of COVID-19.

6. Conclusions and areas for future work

Despite the high widespread of COVID-19 contagion worldwide, there is no specific efficient treatment that has been proved till now. Several pharmacological interventions for COVID-19 have been suggested targeting the host's immune response. Following SARS-coV-2 exposure, there may be an overproduction of GRP within lung tissue resulting in increased release of inflammatory cytokines such as IL-1β, IL-6, TNF-α, VEGF, GM-CSF and MCP-1. Such cytokines are widely known to enhance neutrophil infiltration which, in turn, induce lung inflammation and respiratory distress as reported in COVID-19 infected patients. As well, cytokines release is also presumed to develop SARS-coV-2 - associated pulmonary fibrosis. Novel findings define COVID-19 as one of the pulmonary diseases associated with endothelial and platelets dysfunction. Now, it is definitely known that viral invasion can be mediated by one of the RAS signaling system components, namely ACE-2. Hence, COVID-19 occurrence and progression can be attributed to imbalance in the pulmonary RAS signaling resulting from SARS-coV-2-induced ACE-2 drain. Interestingly, the decrease in ACE-2 activity will be accompanied with a decrease in the generation of Ang1-7 which was known to be the light side of RAS. Regarding the data emphasized on the protective role of Ang (1–7) in lung injury, it may be recommended as a COVID-19 therapy, but because of its short half-life, Ang (1–7) exhibits a limitation for its use. Since NEP is a more potent alternative way than ACE-2 for producing Ang1-7, it is suggested to assess the possible beneficial role of NEP against COVID-induced lung injury. Few studies have discussed NEP-mediated protective pathways in experimental models of lung injury and fibrosis, however its actual role as a lung protective therapy has not been yet recognized. NEP has been involved in degradation of many peptides that may be incorporated in COVID-19 pathophysiology. So, we expect that NEP can effectively interfere with the chemotactic responsiveness and recruitment of neutrophils by degrading both fMLP peptide and GPR, respectively. Furthermore, we suggest that NEP can minimize cytokine storm associated with SARS-coV-2 invasion through inhibiting Ang II formation by neutrophil-derived Cathepsin G and directing Ang I for generating Ang (1–7) which can in turn suppress TGF-β1 expression and its fibrogenic action, protecting against fibrosis. Degrading both BKs and ET-1 by NEP may be associated with low IL-6 levels, which will be beneficial for stabilizing endothelium and restoring its function. In addition to its catabolic properties, we postulate that NEP may possess an advantage for COVID-19 high risk patients through modulating blood pressure and glucose homeostasis. Practically, numerous in-vivo and in-vitro experimental manipulations were made to upregulate NEP expression either by using drugs (Dexamethasone and Valproic acid), hormones (Androgens and Estrogen) or natural substances (Apigenin, Luteolin, Curcumin and (-)-Epigallocatechin-3-gallate). However, others directed their efforts towards preparing the recombinant NEP (r NEP). Because most pre-clinical and clinical studies within the medical field are interested in studying NEP inhibitors, there is a little data concerning use of NEP as a therapeutic agent. Consequently, its associated adverse effects have not yet been studied well. Finally, we hope our hypothesis will be somewhat enough to direct a future work towards the therapeutic role of NEP in modulating COVID-19 pandemic and to target the subsequent therapies for enhancing NEP activity in COVID-19 patients.

Conflict of interest

The authors declare no conflict of interest. The authors and their institutions are the only responsible for the financial support and the content of this work in the submitted manuscript. All other authors have no conflict of interests to disclose.

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