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Translating bioactive peptides for COVID-19 therapy

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ABSTRACT

COVID-19 (Coronavirus disease 2019) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense RNA virus. This virus has emerged as a threat to global health, social stability, and the global economy. This pandemic continues to cause rampant mortality worldwide with the dire urgency to develop novel therapeutic agents. To meet this task, this article discusses advances in the research and potential application of bioactive peptides for possible mitigation of infection by SARS-CoV-2. Growing insight into the molecular biology of SARS-CoV-2 has revealed potential druggable targets for bioactive peptides. Bioactive peptides with unique amino acid sequences can mitigate such targets including, type II transmembrane serine proteases (TMPRSS2) inhibition, furin cleavage, and renin-angiotensin-aldosterone system (RAAS) members. Based on current evidence and structure-function analysis, multiple bioactive peptides present potency to neutralize the virus. To date, no SARS-CoV-2-explicit drug has been reported, but we here introduce bioactive peptides in the perspective of their potential activity against SARS-CoV-2 infection.

1. Introduction

Since its initial presentation in Wuhan, China, COVID-19 respiratory disease has generated enormous global concern and developed into a worldwide pandemic (Lu et al., 2020). Following the identification and isolation of the virus, the World Health Organization (WHO) named the positive-sense RNA pathogenic virus causing COVID-19 as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 represents the seventh coronavirus and the interspecies spread of the virus is considered to be the key cause of the viral epidemic (Wang et al., 2020). The initial studies confirmed that SARS-CoV-2 belongs to the genus Betacoronavirus and with ~79% similarity at the nucleotide level to the earlier SARS-CoV virus (Lu et al., 2020; Wu et al., 2020). Two earlier events of similar nature have occurred in China and Saudi Arabia wherein animal Betacoronaviruse(s) crossovered to humans and resulted in public health emergencies (Memish et al., 2020; Parashar and Anderson, 2004; Singhal, 2020). As COVID-19 spread, the susceptibility of all age groups was evident to infections through inhalation of infectious droplets (Rothe et al., 2020). Further, the virus remains stable on surfaces for days and infection may even be acquired by touching the contaminated areas (Rothe et al., 2020; Singhal, 2020). Clinically, COVID-19 infection may exhibit an asymptomatic state, as well as a wide range of symptoms from mild disease to acute respiratory distress and even multi-organ dysfunction (Chen et al., 2020). However, significantly milder pathogenesis has been observed in neonates, infants, and children, compared to their adult counterparts, yet, as we learn more, this may be an overgeneralization (Chen et al., 2020; Zeng et al., 2020).

At the molecular level, pathogenesis commences with the binding of the virus to cellular receptors, hence, the receptor recognition is a key element of host tropism. Also, the gain-of-function of a virus to attach to the receptor equivalents in other species is a prerequisite for interspecies transmission (Lu et al., 2015). The receptor binding domain (RBD) of SARS-CoV-2, like SARS-CoV, binds with the receptor of angiotensin-converting enzyme 2 (ACE2) (Wrapp et al., 2020). ACE2, a metallopeptidase, since its discovery in 2000, is a well-studied homolog of angiotensin-converting enzyme (ACE), a crucial renin-angiotensin-aldosterone system (RAAS) enzyme (Boehm and Nabel, 2002). It has gained tremendous attention with its ability to convert angiotensin II (Ang II) to angiotensin (1–7), thus attenuating hypertension and mitigating redox stress (Boehm and Nabel, 2002; Wang et al., 2020). Consequently, ACE2 is a leading focus for pharmacological and nutraceutical mediation in numerous pathologies. The latest report shows that the extracellular peptidase domain of ACE2

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meticulously identifies SARS-CoV-2 RBD via its polar residues (Yan et al., 2020). These features make ACE2 and the RAAS system a drug target for mitigation of COVID-19 pathology. Further, another unique feature and drug target of SARS-CoV-2 infection is the inclusion of a polybasic furin-like cleavage site insertion at the junction of the S1 and S2 subunits of the spike (S) protein, possibly increasing the infectivity and mortality due to the virus (Coutard et al., 2020; Wu and McGoogan, 2020). Explicitly, it is also vital to note the participation of the RAAS system in the pathology of COVID-19. Since the beginning of the epidemic in China, studies have outlined the added deaths of hypertensive COVID-19 patients (Wu and McGoogan, 2020; Zhou et al., 2020a). Continued concerns were raised at the beginning regarding treatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which may subsequently raise ACE2, the viral receptor for SARS-CoV-2 (Patel and Verma, 2020). Ambiguously, based on this rationale, ACE2 upregulation may enhance the predisposition to COVID-19 infections although some reports now show that it may be protective against Ang II-mediated pulmonary vasoconstriction and inflammatory activation (Boehm and Nabel, 2002). Dysregulation of ACE2 during SARS-CoV-2 infection has been proposed to also induce disease in non-respiratory organs in the absence of evidence for direct infection of those organs (Böhm et al., 2020). Notably, pulmonary complications are central to COVID-19 (Singhal, 2020; Zhou et al., 2020a). Further, COVID-19 progression is also linked with a severe rise in inflammatory cytokines including GCSF, MCP1, MIP1A, IL2, IL7, IL10, IP10, and TNFα (Chen et al., 2020), many of which are known downstream targets of Ang II (Suzuki et al., 2003). New evidence indeed suggests that a reduction of Ang II after antihypertensive drugs targeting the RAAS system actually contributes to reduced inflammation storm associated with COVID-19 infection (Mehra et al., 2020). Also, three large clinical studies did not support the notion that antihypertensive drugs would worsen the risk of COVID-19 infection or mortality (Mancia et al., 2020; Mehra et al., 2020; Reynolds et al., 2020). Thus, there is a consensus now that hypertensive patients should continue their medications as advised by the attending physician (Mehra et al., 2020; Meng et al., 2020; Vaduganathan et al., 2020). Thus, the complicated nature of COVID-19 pathology and the balance between ACE-2 and Ang II must be addressed in treatments involving the blocking of ACE2 binding. Hence, it is safe to say that ACE2 does not appear as a tidy villain in COVID-19 story. Even some scientists have begun to think the RAAS targeting medicines, even those increasing ACE2, maybe a good therapy for COVID-19 (Sanchis-Gomar et al., 2020). Further, clinicians are now beginning to suspect that an imbalance in Ang II clearance in our bodies, due to ACE2 and SARS-CoV-2 interaction, could be skyrocketing Ang II and propelling cytokine storm mediated inflammation and consequential severe lung and heart damage seen in advanced COVID-19 patients. Although research related to COVID-19 is fast-changing, as of Summer 2020), there is no concrete data from clinical trials that any potential treatment definitively improves clinical outcomes. Overall, the treatment is broadly supportive and symptomatic. This can create pressures on health care systems and professionals as the soaring volume of patients requiring subcritical or critical care can overwhelm healthcare teams, available bed space, and ventilators, even in highly developed countries (Emanuel et al., 2020). In light of the complicated pathology, global health risk, and the time-consuming nature of clinical trials, new approaches to therapeutics against SARS-CoV-2 are essential. As peptidases, proteases, RAAS, and inflammation are central to the pathology of SARS-CoV-2, we propose the consideration and study of peptides with the documented ability to modulate these targets, and minimal adverse effects, as adjuvant treatment of COVID-19. Herein, we review the key drug targets of SARS-CoV-2 and evidence indicating that peptides, based on their amino acid moieties, may merge as a supportive adjuvant utility in treating/preventing COVID-19.

2. Key SARS-CoV-2 targets for bioactive peptides

2.1. ACE2

ACE2 mainly counterweights the vasoconstrictive action of ACE as it generates vasoconstrictive and inflammatory Ang II from Ang I, while ACE2 produces angiotensin (1–7) from Ang II which, moves the equilibrium from vasoconstriction to vasodilation in the vasculature (Donoghue et al., 2000). Despite its close resemblance to ACE, unlike ACE, which removes dipeptides, ACE2 only removes single amino acids, from the C-terminus of a peptide, thus acting as a carboxypeptidase (Crackower et al., 2002; Donoghue et al., 2000). Additionally, ACE2 transforms Ang I to Ang 1–9, which can be translated by ACE to Ang 1–7, as a result, ACE2 constrains the vasoconstrictive and pathological effects of Ang II (Tikellis and Thomas, 2012). Following the COVID-19 epidemic, scientists swiftly established that hACE2 is utilized by SARS-CoV-2 for cellular entry (Zhou et al., 2020b). Studies have also shown that SARS-CoV-2 except in mouse can use the ACE2 receptor as its entry receptor (Zhou et al., 2020b). Also, it is now clear that the ACE2 binding affinity of SARS-CoV-2 is 10–20 fold greater compared with SARS-CoV (Wrapp et al., 2020). ACE2 receptor is prominently found on the surface of alveoli, thus justifying the rampant inflammation and pulmonary involvement in the disease (Singhal, 2020; Wu and McGoogan, 2020). These findings have prompted researchers to solicit changes in hypertensive treatments as some studies suggest that ARBs and ACEIs may possibly raise ACE2 levels. Yet, avoiding the use of ACE2 enhancers or the therapeutic potential of ACE2 inhibitors is doubtful given the evident ACE2 cardioprotection (Cavanagh, 2003). In a seminal review published in Mayo clinic proceedings by Sanchis-Gomar and colleagues, clinicians also didn't support the idea of direct ACE2 blockade in COVID-19 treatment, but endorsed the use of ARBs and suggested finding a unique target(s) (Sanchis-Gomar et al., 2020). Thus, digging deeper into the SARS-CoV-2 entry mechanism, we find that it requires TMPRSS2 for the successful priming of its viral S protein. The S protein of coronavirus undergoes a conformational change following binding to ACE2, which permits proteolytic processing by TMPRSS2, thus enabling viral and cell membrane fusion. The clinical applicability of this unique drug target was confirmed by a recent report showing that a TMPRSS2 inhibitor (camostat mesylate) can block viral entry and maybe a prospective drug (Hoffmann et al., 2020). Therefore, instead of directly blocking ACE2 by using peptides (natural or synthetic), which can cause RAAS imbalance, their application and tailoring towards TMPRSS2 inhibition can help in prevention of the successful viral entry to the cell. Thus, the application of peptides to mitigate successful priming of its viral S protein via their role as protease inhibitors must be explored further. The details of the current evidence and prospective research are discussed in the subsequent section(s).

2.2. Angiotensin II

The human physiology leverages three key vasopressor peptides to maintain systemic vascular resistance *viz*. angiotensin II (Ang II), catecholamines, and vasopressin (Garrison et al., 1979). Of our interest, Ang II is a naturally occurring octapeptide endogenous RAAS hormone with endocrine and vasopressor activities (Fig. 1) (Basso and Terragno, 2001). It induces vasoconstriction through agonism at the Ang II type 1 receptor (AT1R) (Boehm and Nabel, 2002; Brosnihan et al., 2003). Other physiological functions of Ang II include thirst sensation and renal homeostasis (Basso and Terragno, 2001; Struthers and MacDonald, 2004; Tikellis and Thomas, 2012). It is proposed that SARS-CoV-2 binding to ACE2 receptor can diminish remaining cellular ACE2 activity, thus, leaning the ACE/ACE2 balance towards a rampant ACE/Ang-II/AT1 axis signaling, in which Ang II can trigger vasoconstriction, inflammation, and oxidative damage, eventually culminating towards excessive pulmonary injury and distress (Sanchis-Gomar et al., 2020). As the ACE2/Ang 1–7/MasR axis has an opposing effect on the ACE/Ang

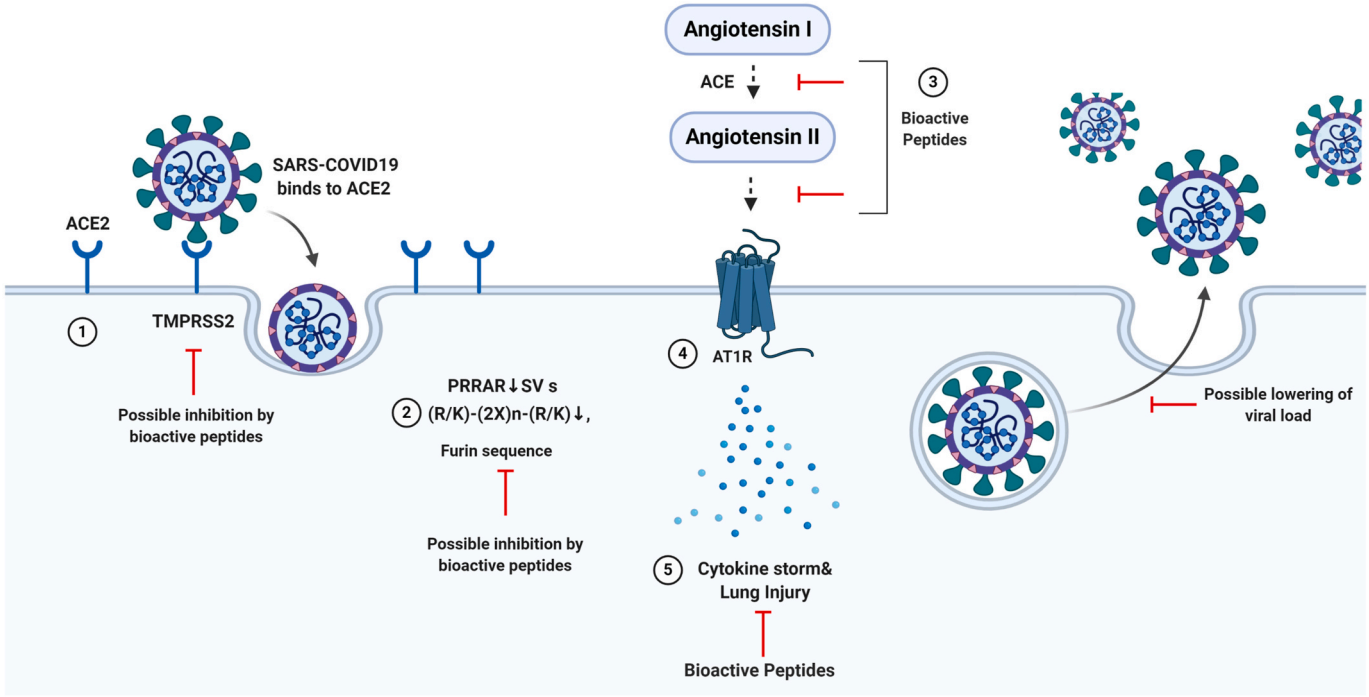

Fig. 1. The potential role of bioactive peptides in mitigation of SARS-CoV-2 pathology.

II/AT1R axis, therefore, targeting of the latter can mitigate downstream redox and vasoconstrictive stress. Essentially, the clinical aim is to attain a balance between how much Ang II is expressed, and how much is accumulated/processed (or managed via drugs). The ARBs have an edge over ACE inhibitors as the latter is linked with higher adverse events and particularly bradykinin and angioedema accumulation prompted cough, which can further spread the virus (Messerli et al., 2018). Overall, it has been hypothesized but unconfirmed that persistent Ang II surge may be in part responsible for pulmonary injury in COVID-19 patients. Therefore, the prospective use of peptides-based Ang II antagonists (AT1R inhibitors) to counterbalance RAAS is a rational pharmacological approach. Similarly, Gurwitz recommended using available AT1R blockers, for instance, losartan, as a pharmacological intervention in COVID-19 infections (Gurwitz, 2020). The details of the current evidence regarding the ability of peptides to counter Ang-II are discussed in the subsequent section(s).

2.3. Furin

The spike glycoprotein of SARS-CoV-2 contains a cleavage site for host cell proteases called furin. This furin cleavage site present in the spike glycoprotein of the SARS-CoV-2 coronavirus is deemed essential for the virus to enter the host cells. This presents it as a novel target for possible attenuation of the viral life cycle and viral load in host cells. At the molecular level, proprotein convertases (PCs) comprise of serine secretory proteases that cleave precursor proteins at specific single or paired basic amino acids (aa) within the motif (R/K)-(2X)n-(R/K)↓, where n = 0, 1, 2, or 3 spacer aa (the downward arrow indicates the site of cleavage) (Seidah and Chrétien, 1999). Owing to their ability to process several critical cell surface proteins, especially furin, PCs have been implicated in viral infections (Izaguirre, 2019). Interestingly, earlier human infecting betacoronaviruses such as HCoV-OC43, MERS-CoV, and HKU1 display the canonical (R/K)-(2X)n-(R/K)↓ motif and their spike protein is cleaved at an S1/S2 cleavage site generating the S1 and S2 subunits (Coutard et al., 2020). As a cellular protease, furin processes a variety of proproteins, and insertion of a furin-like cleavage site in the S-protein sequence has shown to increase the pathogenicity of other viruses (Cheng et al., 2019; Kido et al., 2012). Remarkably, the SARS-CoV-2 S-protein sequence contains 12 additional nucleotides upstream of the single Arg↓ cleavage site 1, which presents PRRAR↓SV sequence, which resembles a canonical furin-like cleavage site (Coutard et al., 2020; Kido et al., 2012). A key paper has shown that the SARS-CoV-2 S-protein sequence has a specific furin-like cleavage site, which was absent in SARS-CoV sequences (Coutard et al., 2020). Therefore, the aim to make anti-SARS-CoV-2 therapeutics must incorporate the evaluation of furin inhibitors. The details of the current evidence regarding the ability of peptides as furin inhibitors are discussed in the subsequent section(s).

3. Current treatment

Presently, there is no explicit and definitive cure for COVID-19. Given the absence of effective antiviral therapy against COVID-19 (Ford et al., 2020), according to the Mayo clinic guidelines, existing treatments mainly focus on respiratory and symptomatic support. Several vaccines and drug candidates that are based on S protein are being assessed. Other potential therapies under evaluation include anti-inflammatory drugs (Zhang et al., 2020), anti-malarial drugs (Colson et al., 2020), convalescent plasma therapy (Shen et al., 2020), traditional Chinese medicine (Ren et al., 2020), viral cycle blockers, virus deactivating antibodies, and small interfering RNAs (Du et al., 2009). Sanders and colleagues have reviewed in detail the current pharmacologic treatments for COVID-19 and concluded that no therapies have been shown curative to date (Sanders et al., 2020). However, mRNA vaccine candidates, first to enter clinical trials, are widely accepted as a major hope for solving the COVID-19 pandemic crisis.

4. Peptides: where do they fit?

As discussed in earlier sections, multiple drug candidates are under intensive investigation for SARS-CoV-2 treatment, the novel coronavirus that caused the COVID-19 pandemic. As the entry of SARS-CoV-2 into a human cell via the ACE2 receptor depends on TMPRSS2 for proteolytic activation of the spike protein, it is vital to analyze bioactive peptides for blocking this biological function. Looking at the literature, we have several pieces of evidence and prospective candidates indicating the

ability of peptides towards inhibition of this host protease. In a peptide-based screening study, TMPRSS2 was found to strongly prefer substrates with an arginine rather than a lysine, and hydrophobic amino acids (particularly, isoleucine) bind to the large hydrophobic S1 pocket of TMPRSS2, which contains its signal peptide (Lucas et al., 2014). Therefore, blocking the key ACE2 and TMPRSS2 processing interaction by peptides substrates containing arginine, isoleucine or leucine is a rational approach for further study. Hundreds of peptides with these amino acids have been studied for their biological function, particularly antihypertensive and antioxidant activity. Therefore, research groups should focus on screening peptides with the TMPRSS2 associated amino acids such as arginine, valine, isoleucine, or leucine for potential TMPRSS2 inhibitory action. Two publications have shown the inhibition of influenza virus spread in TMPRSS2-expressing MDCK cells by treatment with hydrophobic decanoylated peptide mimetic inhibitors (Bertram et al., 2010; Böttcher-Friebertshäuser et al., 2010). Böttcher-Friebertshäuser and colleagues synthesized a peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO), and its treatment lead to the expression of an incomplete and inactive form of TMPRSS2 enzyme (Böttcher-Friebertshäuser et al., 2010). Also, aprotinin, an arginine rich polypeptide of 58 amino acids purified from bovine lung inhibits similar serine proteases (Ovcharenko and Zhirnov, 1994). Likewise, peptides EK1, EK1P, and EK1C potently prevented the replication of SARS-CoV-2 (nM range) (Xia et al., 2020). Similarly, in the latest study, after a screening of 30,927 compounds, 12 natural bioactive compounds with activity against TMPRSS2 have been identified (Rahman et al., 2020). Among these compounds geniposide an iridoid glycoside, exhibited the strongest TMPRSS2 inhibitory activity (via docking) indicating the capability of similar bioactives to inhibit the SARS-CoV-2 binding. These evidence(s) warrant further studies and consideration for clinical modulation of COVID-19 via direct inhibition of TMPRSS2 function using potential peptide or peptide-conjugate protease inhibitors.

It is now well known that several food-derived ACE inhibitory peptides can significantly lower the Ang II production and AT1R expression, and this is property of peptides can help alleviate pulmonary stress in COVID-19 patients. Apart from the upstream approach, which involves decreasing Ang II levels by inhibiting ACE, food-derived peptides can obstruct the downstream pathological Ang II redox and immune stress action as well. Lactoferrin derived tetrapeptide, RPYL has a direct inhibitory impact on Ang II stimulated vasoconstriction via AT1R inhibition (Fernández-Musoles et al., 2014). Three rapeseed protein derived peptides, GHS, LY, and RALP, boost Mas receptor transcription *in vivo*. Among these three peptides, LY, a hydrophobic amino acid peptide substantially downregulated Ang II levels *in vivo* (He et al., 2019). Likewise, in multiple studies, bioactive peptides (in high hundreds) have exhibited the ability to modulate this node of the RAAS pathway. The strongest *in vivo* effects have been observed for short bioactive peptides, such as AYFYPEL, FP, FY, GKP, HLPLP, IPA, IPP, IQW, IRW, IW, LKP, LRW, LW, PYVRYL, RRWQWR, RYLGY, VELTP, VPP, VY, VYP, and YP, with most of them having arginine, proline, tyrosine or tryptophan (Liu et al., 2018; Miralles et al., 2018). Likewise, peptide rich egg hydrolysates reduce AT1R expression as well (Jahandideh et al., 2016). Multiple peptides from other sources like meat (Bhat et al., 2017), marine organisms (Ghanbari, 2019), and plants (Lee and Hur, 2017) have been reported to modulate the ACE/AT1R axis. Their ability to control ACE and AT1R expression possibly depends on the presence of positively charged amino acids along with hydrophobic tryptophan, that can bind to Zn^{2+} at the enzyme active site, controlling its expression (Liao et al., 2018). We only aim to indicate the ability of the peptides in COVID-19 to control pulmonary complications by attenuating ACE and AT1R expression in this article as the sole hypertension-peptide topic is extensively reviewed in the literature (Karami and Akbari-adergani, 2019; Liu et al., 2018). Also, the attenuation of Ang II and Mas receptor surge can lead to an enhancement of the pulmonary function in COVID-19 patients as well. As some peptides have been reported to increase ACE2, which can either possibly favor the virus entry or reversing the lung injury, however, it is contingent on the exact time and nature of peptide-based treatment. As discussed above, some ARBs which can prospectively increase ACE2 have not been discontinued in clinical settings, therefore the use of these peptides can certainly help with ancillary pharmacotherapy (Sanchis-Gomar et al., 2020).

Next, furin and related furin-like PCs cleave their substrates at distinctive sequences, favorably after an arginine residue. Previously, by the inclusion of decarboxylated arginine mimetics in substrate analog peptidic inhibitors helped to discover and develop highly potent furin inhibitors (Becker et al., 2010). Arginine rich phenylacetyl-Arg-Val-Arg-4-amidinobenzylamide inhibits furin with a K_i-value of 0.81 nM, interestingly containing sequence similar to bioactive peptides (Becker et al., 2010). Polyarginines are effective, small furin inhibitors (Cameron et al., 2000), and successful inhibition of furin by polyarginine-containing peptides have been achieved as well (Kacprzak et al., 2004). The activity of these peptides and similar compounds may be based on their interaction for the reactive center R^{355}-I-P-R^{358}-$\downarrow$ or to form a kinetically trapped Sodium Dodecyl Sulphate-stable complex with the enzyme (Jean et al., 1998). In this study, dec-RVKR-cmk ($k_i = 2$ nM), an arginine containing furin inhibitor completely blocked the furin cleavage reactions (Jean et al., 1998). Likewise, the administration of hexa-d-arginine blocks the activation of pathogenic microbial toxins via furin inhibition (Sarac et al., 2002). Another study showed that the insertion of "enediynyl amino acid" between P1 and P1' residues of hfurin$^{98–112}$ peptide inhibited furin with IC_{50} ~40 nM (Basak et al., 2009). The hfurin$^{98–112}$ residues contain QQVAKRRTKRDVYQE amino acids, of which multiple arginine residues may be involved with inhibition of furin. These studies strongly indicate that arginine containing bioactive peptides should be screened for furin inhibition as previous evidence warrant their mechanistic applicability.

To date, no peptide-based study has been conducted to see their impact on SARS-CoV-2 therapy via these drug targets. Precision based tailoring of peptide design is a sound strategy to explore the stated drug targets. Strong evidence is already available to support their use as modulators of the ACE/AT1R axis. Further, a careful screening of peptides with desired amino acids, particularly arginine, valine, leucine, and isoleucine could yield peptides with TMPRSS2 or Furin inhibitory activity, while constraining the Ang-II production as well.

5. Discussion and perspectives

Except for HCoV-OC43 and HKU1, four CoVs identify proteinaceous peptidases as the cell entry receptors (Li et al., 2005). While belonging to separate taxonomical genera, both SARS-CoV and hCoV-NL63 interact with ACE2 for cellular entry (Singhal, 2020). For the SARS-CoV-2 to successfully enter the cell(s) following the initial interaction, the spike protein has to be primed by TMPRSS2 (Guo et al., 2020; Hoffmann et al., 2020). This step presents itself as a unique drug candidate to inhibit the complete entry of the virus to the cells, particularly alveoli. We propose that arginine, valine, isoleucine, or leucine containing peptides may serve as an alternate substrate for TMPRSS2. Perhaps we can examine some important lessons from the use of these peptides in experiments, to confirm or reject our hypothesis and inform our attempts going forward. For instance, if successful in inhibiting TMPRSS2, can these peptides be used for all COVID-19 patients? Or should they be considered earlier in the course of the disease, perhaps as a preemptive/prevention strategy? Finally, and more controversially, should we evaluate the pharmacological effects of possibly ACE2 stimulatory peptides on TMPRSS2 activity? For example, transcriptomics studies have recently shown that peptides such as IRW, derived from ovotransferrin and AKSLSDRFSY, LSDRFS, and SDRFSY, derived from pea can increase ACE2 levels (Liao and Wu, 2020). These peptides do contain amino acids of our interest for modulating TMPRSS2, but the possible increase in ACE2 needs to be observed as well. We also propose the use of peptide analogs of such peptides to be screened for their ability to inhibit or lower TMPRSS2.

Theoretically, an increase in ACE2 levels by these peptides may present a drawback, but given the enormity of the current situation, we are obligated to explore unique drug candidates, particularly substrate mimetic peptides as a potential avenue of treatment.

From studies on other viral diseases and their treatment, a furin inhibitory method might be feasible, although not devoid of limitations. Currently, most of the evidence supports the efficacy of furin inhibitors; however, partial clinical evidence supports or refutes their use. One application of furin inhibition stands out, i.e. the development of a cancer vaccine, which employs furin knockdown to extend therapeutic action (Senzer et al., 2012). As we discussed earlier, peptides, particularly those containing arginine residue have a potential act on furin-like cleavage sites in the SARS-CoV-2 S-protein sequence. The peptide candidates should be able to inhibit furin in the infected cells as well as and at the surface of the uninfected cells. Therefore, to discover the peptide-based candidates, it is vital to identify the peptides that can act both on the cell-surface and also reach intracellular space. Hence, the selection of peptides with proven cell penetration and bioavailability from *in vivo* studies may present some favorable results. Previously established furin inhibitors support this idea of cell penetration as well (Garten et al., 1989; Kibler et al., 2004). Once, a peptide based furin inhibitor is identified, its efficacy can be increased by several approaches, including the design of novel analogs with new terminal moieties and inclusion of D-amino acids instead of L-amino acids (Sarac et al., 2002). Next, a possible obstacle for the development of peptide-based furin inhibitors is their potential off-target consequences as complete furin knockout in mice is lethal. However, it is indeed possible that acute and controlled and precise inhibition may ensue valuable clinical output. Although the development of peptide-based furin inhibitors may be full of pitfalls, yet it is a promising approach that should be further pursued in the quest for treatment of COVID-19.

Finally, the modulation of the RAAS pathway, particularly Ang II and AT1R blocking is already an accepted approach. The underlying premise is the potential dysregulation of the Ang II/AT1R pathway could lead to cytokine release syndrome, particularly the IL-6-STAT3 axis, as observed in COVID-19 patients. Also, at the beginning of the COVID-19 pandemic, it was proposed that patients with hypertension may be at an increased risk due to ACE2 enhancing ARBs, however, it is still debated in the clinical community (Patel and Verma, 2020; Sanchis-Gomar et al., 2020; Yan et al., 2020). This premature assumption generated confusion in the research and medical community. Although, leading commentaries suggest that the impact of RAAS drugs on the outcome of COVID-19 needs to be determined urgently (Sommerstein et al., 2020). In this line a recent study found that ACEi/ARBs use has no negative impact on 895 hypertensive patients with COVID-19, thus no evidence was found for discontinuation of ACE2 enhancing ACEi/ARBs in the milieu of the COVID-19 epidemic (Fosbøl et al.). The presence of selection bias, unmeasured confounding, and time bias makes their discontinuation a weak case (Quinn et al., 2020). Multiple hypertension and cardiology societies have now reinforced that there is not enough information to either block usage of ACE2 activating ACEi/ARBs in wake of COVID-19. A recent NEJM article also suggested continued use of RAAS modulators, like AT1R inhibitors and ACEi, which may increase ACE2 theoretically and affect the propensity for or severity of COVID19 (Vaduganathan et al., 2020). Also, many questions about ACE2 remain unclear and are being rigorously investigated in ongoing trials. As this clinical equipoise exists, we suggest reducing Ang II and AT1R to ease pulmonary severity in COVID-19 patients or those not yet showing such patterns may represent a valuable therapeutic option. Also, some preclinical evidence suggests that RAS blockade might attenuate progression of COVID-19 (Tignanelli et al., 2020), yet, there is an urgent requirement for multicentre clinical trials to test this hypothesis. Regarding ACE2, the application of soluble ACE2 fragments, ACE2 antibodies, recombinant ACE2, and Ang 1–7 peptides may provide alternate therapeutic approaches (Jiang et al., 2020). Of note, bioactive peptides which inhibit ACE/AT1R can perhaps prevent downstream IL6-STAT3 burst as well, as by steroids, and selective immune modulators (eg, anakinra or tocilizumab) and JAK pathway inhibition in the clinic (Mehta et al., 2020). There is more than a decade of *in vivo* evidence supporting bioavailability and efficacy of peptides for modulating RAAS and inflammation. Therefore, their application owing to their *in vivo* efficacy and the non-deleterious effect is strongly merited.

Finally, the future of SARS-CoV-2 virus biology offers unique drug targets for its treatment. Any adaptation or mutation in the COVID-19 sequence might even make it more virulent or resistant to drugs (Martinez, 2020). Contrarily, SARS-CoV-2 is also be projected to lose virulence via human transmissions due to genetic bottlenecks for RNA viruses that frequently occur during the transmission of infectious respiratory droplets (Cascella et al., 2020). Further, in the last 10 years, significant advancement has been made in the field of peptide pharmacology using chemical and biological techniques. Sincere efforts are required to translate the current pharmacological evidence of peptides to 'druggable' molecules with enhanced potency. Such drugs have been effectively used in the clinic, but it is still challenging for food-derived bioactive peptides to achieve clinical acceptance. A major challenge is the lack of understanding regarding the mechanisms underlying their pharmacological effects, as their impact is not usually based on one molecular target. Besides, classical drug design and computational methods primarily focus on a single target. Regardless of these challenges, bioactive peptides reviewed here to highlight their therapeutic relevance in mitigation of SARS-CoV-2 pathology. Global health and drug/nutraceutical discovery will never be the same after the COVID-19 pandemic, it cannot be. We should no longer pay lip service to alternative and innovative interventions in the mitigation of COVID-19. Whether novel natural bioactive or rationally designed peptides, they must be explored further. In conclusion, bioactive peptides are perhaps not the definitive answer to the COVID-19 pandemic; however, they exemplify a rational, viable, and hopeful longstanding approach for COVID-19 remediation.

6. Limitations

This review article has numerous limitations. First, the fast-paced research on the treatment of COVID-19 is not fully discussed as it is constantly evolving every day. Second, there is limited published data on bioactive peptides and COVID-19, expect one opinion paper (Goudarzi et al., 2020). Third, our review focused only on peptides with potential activity on selected activity based on structure-function and target sequence. Fourth, the articles studied for this review were limited to English journals, so pertinent international data may be missing. The tentative suggestion to apply bioactive peptides with specific amino acids based on selected targets as SARS-CoV-2 therapeutics for treating mild or moderate patients remains unproven until tried.

7. Conclusions

At the time of penning this brief article, the end or even a tentative drug for the COVID-19 epidemic is not in sight and radical ideas and actions are required for identifying therapeutic molecules. Hence, a rational approach is to identify novel/potential drug targets and search the literature and test candidates to counter SARS-CoV-2 pathology towards better disease outcomes. Bioactive peptides, owing to their bioavailability, pharmacological efficacy, and low off-target activity have a strong potential to mitigate the SARS-CoV-2 pathology at different targets. Some of the potential targets include TMPRSS2, furin, and AT1R inhibition for arginine, valine, isoleucine, or leucine-rich peptides. Even if one of the targets is exploited by a peptide, this would support further exploration of peptide antagonists with improved efficacy against SARS-CoV-2.

8. Additional disclosure

The authors of this publication do not advice or suggest any change in standard care and medications of COVID-19 or hypertension patients. Our article solely suggests exploring dietary peptides for research purposes, which may open a new venue of research towards developing COVID-19 therapy. The content of this publication also does not necessarily reflect the views or policies of the affiliated institutions, nor does any mention of trade names, commercial products, nutraceuticals, or organizations imply endorsement by any pharmaceutical or food corporation.

Declaration of competing interest

Steven J. Drews has acted as a content expert for respiratory viruses for Johnson & Johnson (Janssen). The authors declare no other conflict of interest.

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