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Review Article

Therapeutic Approaches in COVID-19 Patients: The Role of the Renin-Angiotensin System

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Two and a half years after COVID-19 was first reported in China, thousands of people are still dying from the disease every day around the world. The condition is forcing physicians to adopt new treatment strategies while emphasizing continuation of vaccination programs. The renin-angiotensin system plays an important role in the development and progression of COVID-19 patients. Nonetheless, administration of recombinant angiotensin-converting enzyme 2 has been proposed for the treatment of the disease. The catalytic activity of cellular ACE2 (cACE2) and soluble ACE2 (sACE2) prevents angiotensin II and Des-Arg-bradykinin from accumulating in the body. On the other hand, SARS-CoV-2 mainly enters cells via cACE2. Thus, inhibition of ACE2 can prevent viral entry and reduce viral replication in host cells. The benefits of bradykinin inhibitors (BKs) have been reported in some COVID-19 clinical trials. Furthermore, the effects of cyclooxygenase (COX) inhibitors on ACE2 cleavage and prevention of viral entry into host cells have been reported in COVID-19 patients. However, the administration of COX inhibitors can reduce innate immune responses and have the opposite effect. A few studies suggest benefits of low-dose radiation therapy (LDR) in treating acute respiratory distress syndrome in COVID-19 patients. Nonetheless, radiation therapy can stimulate inflammatory pathways, resulting in adverse effects on lung injury in these patients. Overall, progress is being made in treating COVID-19 patients, but questions remain about which drugs will work and when. This review summarizes studies on the effects of a recombinant ACE2, BK and COX inhibitor, and LDR in patients with COVID-19.

1. Background

The renin-angiotensin system (RAS) plays an important role in the regulation of the cardiovascular system. Angiotensin II (Ang II) is one of the main products of RAS produced from angiotensin I (Ang I) under the action of the angiotensin conversion enzyme (ACE). Ang II acts via the AT1 receptor, leading to vasoconstriction, direct and indirect reabsorption of sodium through the kidneys, releasing vasopressin and stimulating the hypothalamus's thirst center [1]. All these effects are essential in emergency conditions to maintain the blood flow of vital organs within normal limits. However, a high concentration of Ang II for a long period may cause cardiac hypertrophy and fibrosis, endothelial dysfunction, thrombosis, atherosclerosis, and arrhythmia [2]. Stimulating the AT2 receptor has the opposite effects of the AT1 receptor, like vasodilation and lowering blood pressure (BP) [3]. Ang II is converted into Ang 1–7 by ACE2, a transmembrane enzyme with carboxypeptidase terminal activity. Ang 1–7 acts through Mas receptors and has a counter-regulating action, leading to vasodilation and reduced parameters such as BP, cardiac hypertrophy, fibrosis, thrombosis, and arrhythmia [2–4].

COVID-19 was first detected in China and quickly spread across the globe [5]. It is mainly characterized by cold symptoms that last for a few days. However, moderate to severe COVID-19 can be associated with acute pulmonary inflammation, cardiovascular failure, and coagulopathy. Despite large-scale vaccine programs and a variety of therapeutic approaches used in the treatment of COVID-19 patients, morbidity and mortality remain high. RAS plays an important role in inflammatory reactions, clot formation,

and COVID-19-related virus infections [6–8]. The imbalance between the two arms of RAS (classical and protective arms) contributes to cytokine storm, hypercoagulability, and multiple organ damage in COVID-19 patients [8–11] (Figure 1). The pathogenesis of COVID-19 is related to a novel SARS coronavirus (SARS-CoV-2) that, like previous coronaviruses, enters host cells through ACE2 [12, 13]. Expressions of ACE2 have been described in many organs of the body, including the kidneys, fat tissue, the gastrointestinal tract, the heart, and airway epithelial cells [14–18]. ACE is a key enzyme for the inactivation of bradykinin (BK), while ACE2 breaks down the active metabolites of BK [19]. As a result, downregulation of ACE2 can accumulate active BK metabolites and worsen inflammatory reactions in patients with COVID-19. In addition, a relationship between cyclooxygenase (COX), a key enzyme of inflammation, and RAS has been suggested in COVID-19 patients [20]. A few studies also report the benefits of low-dose radiation (LDR) in the treatment of patients with COVID-19. However, radiation therapy can increase Ang II, the active metabolites of BK, and COX-2, which has an adverse effect on body tissues [21–24]. In this review, we discussed the studies related to the effects of recombinant ACE2, inhibitors of BK and cyclooxygenase (COX), and low-dose radiation (LDR), and their interactions with COVID-19 infection are summarized in Figure 2.

2. Interaction between ACE2 and SARS-CoV-2

Investigation of the interaction between coronaviruses and ACE2 in humans dates back to 2003 when it was reported that the SARS coronavirus (SARS-CoV) entered cells via ACE2 [25–27]. In 2004, the amino acid fragment of the virus's S protein that binds to ACE2 was identified [28]. Moreover, the outbreak of the disease in 2003–04 was shown to be lower than in 2002–03 due to the lower affinity of SARS-CoV protein to ACE2 protein [29]. In addition, it was demonstrated that SARS-CoV-2 can infect several cell types and immune cells, depending on the level of expression of ACE2 [30]. Several therapeutic approaches were recommended to reduce viral cell penetration or complications of the disease. Soluble recombinant human ACE2 (hrsACE2) was suggested to hide the SARS-CoV binding site, thereby preventing the virus from entering cells. [31]. In addition, a number of antibodies, peptides, and small compounds were introduced to slow viral replication, blocking the binding site of the S protein, or inducing conformation into the S protein [27, 32, 33]. However, a number of investigations were discontinued due to a decline in the incidence the disease in 2004.

3. Interaction between COVID-19 and ACE2

Two forms of ACE2 have been identified: cellular (cACE2) and soluble (sACE2). SARS-CoV-2 enters the cells through cACE2 and downregulates transmembrane protein [8]. Furthermore, the expression of ACE2 decreases in patients with COVID-19 [34]. There is a negative correlation between the ACE2 expression and the COVID-19 mortality rate [35]. The entrance of SARS-CoV-2 into host cells is blocked by serine protease TMPRSS2 inhibitors [36]. TMPRSS2 is shown to facilitate the entry of the virus by the S1 and S2 cleavages of SARS-CoV-2 [20, 37]. There are also other proteases that can play roles in SARS-CoV-2 internalization [37, 38]. Furthermore, the ADAM-17 protease releases ACE2 in a soluble form (sACE2) that circulates in the extracellular environment [39]. sACE2 has no membrane anchor used as a cell entry point for SARS-CoV-2 [8, 10]. Therefore, it is suggested to be a therapeutic target to prevent viral entrance in host cells. Studies on Vero cells and kidney organoids can confirm the role of hrsACE2 in preventing cell entry and replication of the virus [40, 41]. However, one study has raised the hypothesis that the effect of sACE2 on viral entry is dose-dependent: sACE2 with physiological concentration leads to viral entry through AT1 and vasopressin receptors, while, pharmacologic concentration may have an inhibitory effect [42]. Furthermore, the use of engineered extracellular vesicles (EVs) exposed to cACE2 and TMPRSS2 is demonstrated to be much more effective than the use of sACE2 for viral trapping and reduction of infection [43] (Table 1). It is important to mention that a high concentration of hrsACE2 is tolerated in ARDS patients without significant side effects [44]. As a result, a high concentration of hrsACE2 may influence COVID-19 patients with ARDS. In a case report study, an intravenous infusion of hrsACE2 twice daily for seven days was well tolerated in a 45-year-old woman with COVID-19. The patient survived until she was discharged on day 57 [45] (Table 2). There are also some review papers proposing the treatment of COVID-19 patients with hrsACE2 [9, 10, 46–48]. Plasma from patients who have recovered from COVID-19 may be an excellent source of neutralizing antibodies against the virus [49]. Soluble ACE2 has also been detected in plasma and may be of value in predicting COVID-19 outcomes [50]. Depending on the concentration of sACE2, sera from highly exposed uninfected subjects could more effectively neutralize SARS-CoV-2 infection in cellular assays, even in the absence of sufficient anti-CoV-2 IgG antibodies [51]. However, additional clinical studies are necessary to explore the effect of sACE2 as a promising therapeutic target on patients with COVID-19.

The downregulation of cACE2 increases the impact of ACE and Ang II in the body of COVID-19 patients. A cohort study showed that Ang II increases in the blood of patients suffering from COVID-19 [52]. It has been reported that hospitalized hypertensive COVID-19 patients who use ACE or AT1 antagonists had a lower risk of mortality than the others [53, 54]. Furthermore, COVID-19 patients with hypertension treated by Ang II receptor inhibitors are less likely to develop severe lung disease [55]. On the contrary, other studies did not show a difference between using ACE or AT1 inhibitors and COVID-19 severity markers [56–59]. In addition, a case-population study has indicated that the administration of RAS inhibitors does not increase the risk of COVID-19 for admission to the hospital and intensive care unit [60]. Moreover, there is no correlation between the administration of RAS inhibitors and the mortality rate in COVID-19 patients [61].

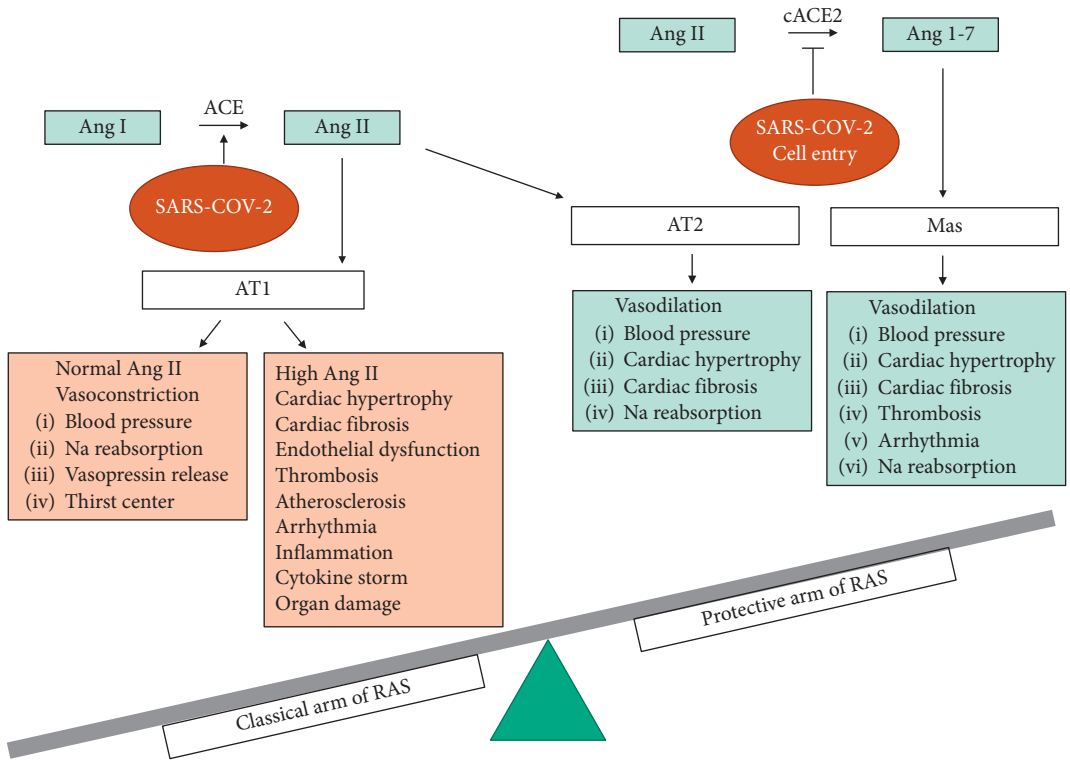

Figure 1: The imbalance in two arms of the renin-angiotensin system in COVID-19 infection: the classical arm vs. the protective arm.

Other researchers also believe that treatment with RAS inhibitors should not stop in COVID-19 infections [62]. In general, the effects of RAS inhibitors on COVID-19 may be affected by the complexity of the pathophysiology of the disease. Furthermore, studies suggest that increased Ang II in a hypoxic environment may activate cancer pathways and tumorigenicity in body tissues, which should be considered in the future follow up of severe COVID-19 patients [63].

4. Interaction between COVID-19, BK, and ACE2

BK is an active polypeptide released by the kinin-kallikrein system (KKS) from damaged tissues. BK is produced from kininogens through kallikrein enzymes and converts to Des-Arg-BK (DABK) and other metabolites by kininase I and kininase II (ACE). DABK is one of the active metabolites of BK, which is hydrolyzed by ACE2 [19, 64–67]. BK and DABK may cause local vasodilation or vasoconstriction through B2 and B1 receptors, whereas both of them may decrease the mean systemic blood pressure. Mechanisms are related to species, vessels, and their downstream signaling pathways such as NO, cyclooxygenase (COX) products, and prostaglandins [68–70]. There are some interactions between RAS and KKS within the cardiovascular system. ACE inhibitors increase the blood levels of BK and Ang 1–7. BK may potentiate the effect of Ang 1–7 in the cardiovascular system and lead to vasodilatation and decreased BP [71]. The mechanism of this interaction can be related to the generation of NO [72]. In contrast, stimulation of B2 receptors potentiates the constrictive effect of the AT1 receptor on small mesenteric vessels in endotoxemia. This finding suggests the presence of AT1/B2 receptor heterodimers that lead to a strong contractile response to BK and Ang II [73].

KKS is a major component of inflammatory reactions and intrinsic coagulation pathways [74]. Inhibition of ACE2 during inhalation of endotoxin increases BK axis activity, neutrophil infiltration, and severe inflammation in the mouse lung [67]. BK is indicated to induce lung damage in ischemia-reperfusion and inflammation caused by parainfluenza-3 [75, 76]. A significant increase in BK and DABK increases vascular permeability, inflammatory reactions, and lung injury, leading to a serious illness called BK storm [77–79]. In addition, both Ang II and KKS stimulate plasminogen activator inhibitor-1 and clot formation, while Ang 1–7 has anti-inflammatory and antithrombotic effects [77, 80]. The relation between BK and COX activity has been reported in several experimental contexts. Inhibitions of the B2 and COX-2 receptors have an additive effect in reducing tissue damage [81, 82]. Therefore, these combination therapies can be useful for patients with COVID-19.

Alveolar epithelial cells express transcripts encoding proteins that play essential roles in the regulation of the KKS, RAS, and coagulation system [83]. In one case-control study, it was reported that the use of the icatibant B2 antagonist improved oxygenation in COVID-19 patients [84]. Furthermore, one randomized clinical trial reported that icatibant and Cle/kallikrein reduce the complications of COVID-19 and the duration of hospitalization (Table 2) [85]. Also, the administration of recombinant neprilysin, as an alternative ACE-2/Ang 1–7/Mas receptor axis, has a

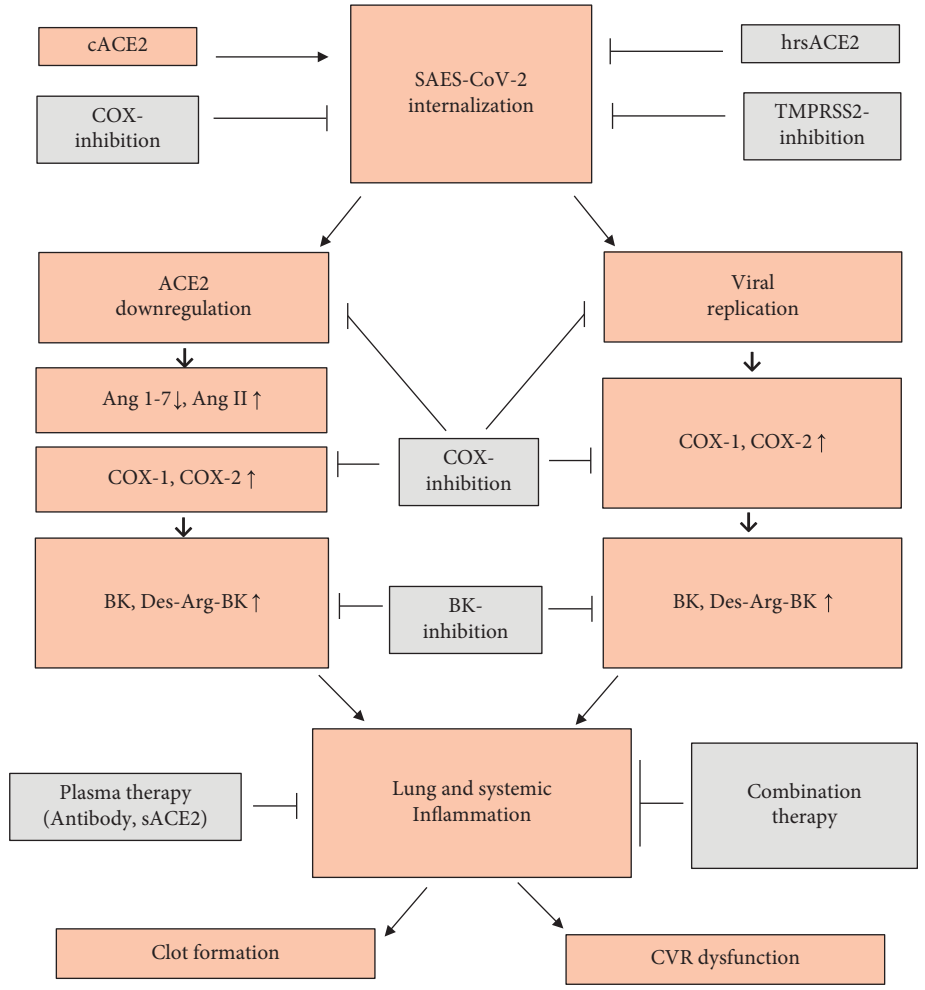

Figure 2: The relationship between sACE2, BK, and COX inhibitor, and plasma therapy in the patients with COVID-19. CVR: cardiovascular.

Table 1: The effect of recombinant ACE2 in SARS-CoV-2 infection in vitro.

Study/subject	Drugs or exposure	Time of treatment	Outcome
Extracellular vesicles (EVs) exposing cACE2	1) SARS-CoV-2 2) TMPRSS2	First phase :1.5 h second phase: after 24 h	(i) Effective in vesicular viral trapping (ii) More efficient: cACE2 with TMPRSS2 [43]
Vero cells (monkey), human blood vessels, and kidney organoids	1) Clinical grade of hrsACE 2) and murine rsACE2: different concentrations	1 hour followed by washing, or 15 h without washing	Block the cell entry of SARS-CoV-2 [41]
Vero E6 cells (monkey) and kidney organoids	1) hrsACE2 APN01 (50–800 μg/ml) 2) Remdesivir (4–80 μM)	Kidney organoid: after 3 days Liver spheroids: after 15 h Measurement of cytotoxicity: after 24 h	Block the cell entry and replication of SARS-CoV-2 [40]
Renal cell line of HK2 (human) and Vero E6 cells (monkey)	1) Different concentrations of rACE2	3 days treatment	High concentration: inhibition of SARS-CoV-2 cell entry Physiologic concentration: increased viral cell entry [42]

higher activity than ACE to BK degradation, and suggest for the treatment of COVID-19 patients [86]. Also, one of the side effects of ACE inhibitors, coughing, is associated with BK accumulation and may exacerbate symptoms in COVID-19 patients [87, 88]. It is also suggested that the use of KKS and BK inhibitors can be considered a therapeutic approach

Table 2: Drug administration in patients with COVID-19.

Study/Subject	Drugs and doses	Time (T) and duration (D) of treatments	Outcome
BK inhibition			
Man and woman (case-control)	1) 3 doses of 30 mg of icatibant (B receptor blocker of BK) by sc injection at 6-hour intervals 2) Standard medications	(i) T: at the onset of admission to hospital (ii) D: 18 h (3 times each 6 hours)	A significant reduction in oxygen supplementation [46]
Man and woman (randomized trial protocol)	1) Icatibant 30 mg subcutaneously, 3 doses 2) The inhibitor of C1e/kallikrein 20 U/kg, i.v on day 1 and 4 3) Standard medications	(i) T: ≤12 days since the onset of the symptoms (ii) D: 4 days	Reducing the complications caused by COVID-19 pneumonia and duration of hospitalization [84]
COX inhibition			
Man and woman (prospective cohort study)	1) Different NSAIDs 2) Standard medications	(i) T: acute: day1 chronic: before COVID-19 (ii) D: different	Mortality and hospital admission did not differ in acute and chronic treatments [85]
Man and woman (prospective cohort study)	1) Different NSAIDs 2) Standard medications	(i) T: different (ii) D: within 14 days before hospital admission	It was not associated with higher mortality or increased severity of disease [94]
Man and woman (retrospective cohort study)	1) Different NSAIDs 2) Standard medications	T: different D: different	(i) Effective in mild disease (ii) COX-2 inhibitor was effective in severe disease (iii) Nonselective COX inhibitors had worse effects [107]
ACE2			
45-year-old woman (case report)	1) Soluble recombinant ACE2 (APN01), 0·4 mg/kg) 2) Hydroxychloroquine, FIO2 of 70%, intubation, mechanical ventilation, cefuroxime, aztreonam	(i) T: 9 days after the onset of symptoms (ii) D: 5 minutes infusion twice a day lasting for 7 days	ACE2 was well tolerated with no obvious side effects [97]
Low-dose radiation			
Man and woman (clinical trial)	1) Whole lung irradiation 2) National protocol for the management of COVID-19	Radiation in a single fraction of 0.5 Gy	Encouraging results for oxygen dependency in 3 of 5 patients [104]
Man and woman (clinical trial)	1) Whole lung irradiation	A single-fraction radiation dose of 1.5 Gy	No worsening of the cytokine storm was observed in 4 of the 5 patients [105]

for the patients with COVID-19, even prior to the administration of a COX inhibitor [79, 84].

5. Interaction between COVID-19, COX-2, and ACE2

Increased activity of COX-2 has been indicated in numerous experimental preparations such as lung injury induced by mechanical ventilation [89]. Inhibition of COX-2 is protective against lung damage caused by LPS in mice [90]. COX-2 inhibitors have antiviral and anti-inflammatory effects [91]. COX-2 inhibitor indomethacin has also been reported to be useful in treating the early stages of SARS-CoV-2 infection in dogs [92]. Moreover, the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen and meloxicam, inhibits the production of proinflammatory cytokines and antibodies against SARS-CoV-2 infection in mice. However, it does not affect ACE2 expression, viral entry to cells, or viral replication in vitro or in vivo [93]. Another study reported that ibuprofen facilitates membrane ACE2 cleavage through the activation of ADAM-17 and prevents membrane-dependent virus entry into the cell by lowering the expression of TMPRSS2 [20]. Consequently, the antiviral effects of ibuprofen may be caused by its direct inhibitory effect on proinflammatory mediators, and indirectly, through its impact on the ACE2 cleavage within the cell membrane [20]. However, a decrease in cACE2 in patients with COVID-19 may augment the activity of the first arm of RAS and downstream COX-related inflammatory pathways, which must be explored in future studies on COVID-19 infection.

Data from two prospective cohort studies reported in Table 1 support the use of COX-2 inhibitors in patients with COVID-19. One study revealed that acute or chronic use of ibuprofen and other NSAIDs is not associated with worsening COVID-19 outcomes [94]. Celecoxib, a selective COX-2 inhibitor, is useful for the short-term treatment of patients with COVID-19 without worrying about major cardiovascular side effects [95]. Diclofenac is recommended as the best COX-2 inhibitor in the treatment of patients with COVID-19 at therapeutic doses [91]. Indomethacin is effective at reducing cough caused by BK during COVID-19 [96]. Meanwhile, a retrospective study found that NSAIDs, particularly selective COX-2 inhibitors, influence mild and severe COVID-19, while nonselective COX inhibitors have worse effects [97]. These findings indicate that the use of selective COX-2 inhibitors is essential for the treatment of patients with COVID-19. In addition, the use of NSAIDs in COVID-19 could reduce the natural host reactions necessary to fight viral infection and mask signs of infection [98].

6. Effects of Radiation Therapy on ACE, Bradykinin, and COX in COVID-19

Radiation therapy has been used to treat cancer and damaged tissue. However, the level, duration, and severity of damaged organs can predict the outcomes of the intervention. Basically, radiation acts as a double-edged sword. On the one hand, the anti-inflammatory effect of LDR has been identified in various experimental settings as well as in patients. However, even LDR can damage some organs like the heart, lungs, and kidneys. The monocyte adherence to the endothelium of the rat aorta increases by 1 to 24 hours after X-ray radiation with a dose of 2.5 Gy, whereas radiation with a dose of 7.5 Gy had no effect because of monocyte damage [99]. It has been demonstrated that radiation-induced heart disease is associated with the activity of the Ang II-aldosterone axis [100]. AT1 receptor antagonists and ACE inhibitors are effective in treating lung and kidney injuries after radiotherapy [21, 22]. Besides, LDR of 0.5 Gy with gamma-ray downregulates B2 receptors in HF-15 cells and consequently reduces inflammation [23]. These data suggest that the inflammatory or anti-inflammatory effects of B2 receptors are influenced by radiation levels and cell types. In addition, COX-2 can be activated by gamma radiation in PC-3 cells, dose dependently, which is inhibited by COX—an inhibitor of NS-398 [24].

A few studies have suggested the beneficial effects of low-dose radiation therapy in patients suffering from COVID-19 [101–103]. Two clinical trials with a small population revealed that 05–1.5 G of LDR led to low oxygen dependency of patients or no worsening of cytokine storm in COVID-19 patients, though extensive population studies are required for validation [104, 105] (Table 2). ARDS can be associated with a reduction in the number of leukocytes in blood, which can have a detrimental effect on the immune system. In addition, it takes 24 hours for radiation to have a maximum effect on macrophages. Therefore, it could not be recommended for treating COVID-19 patients with critical conditions [106].

7. Conclusion

Effective therapeutic approaches alongside global vaccination are needed to overcome such a challenging pandemic. The renin-angiotensin system appears to play a central role in the inflammatory response and cardiovascular disease in COVID-19 patients. Data from this review demonstrate that the timing of medication and disease severity are important for outcomes in patients with COVID-19. The use of BK and COX inhibitors can be recommended as a first step to prevent early inflammatory responses. Recombinant ACE2 can be administered to prevent increased viral internalization and replication, but several preclinical studies should be conducted before clinical trials in COVID-19 infection for final validation. Additionally, low-dose radiation may not be an option in severe COVID-19 patients. Moreover, combination therapy of recombinant ACE, BK inhibitors, and COX inhibitors should be evaluated in more animal models and large-scale clinical trials in the future. Of course, our study does not exclude multiple drug therapies for COVID-19 patients, but due to the wide spectrum of drug therapies, we investigated drugs that are somehow related to the renin-angiotensin system.

Abbreviations

ADAM-17: A disintegrin and metalloprotease 17
Ang I: Angiotensin I
Ang II: Angiotensin II
Ang 1–7: Angiotensin 1–7
ACE: Angiotensin-converting enzyme
ACE2: Angiotensin-converting enzyme 2
AT1: Angiotensin receptor 1
AT2: Angiotensin receptor 2
ARDS: Acute respiratory distress syndrome
BP: Blood pressure
BK: Bradykinin
B1 receptors: BK receptor 1
B2 receptors: BK receptor 2
COVID-19: Coronavirus disease 2019
COX: Cyclooxygenase
DABK: Des-Arg-bradykinin
KKS: Kinin-kallikrein system
Gy: Gray
LDR: Low-dose radiation
NSAIDs: Nonsteroidal anti-inflammatory drugs
hrsACE2: Human recombinant soluble protein ACE2
RAS: Renin-angiotensin system
SARS-CoV: SARS coronavirus
TMPRSS2: Transmembrane protease, serine 2.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

FK and SJ prepared the draft, and FK finalized the paper. All authors read and approved the final manuscript.

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