Review
Published: 2026-06-15
https://doi.org/10.64253/042026jept002

Targeting ACE2 in the Renin–Angiotensin–Aldosterone System: Post-COVID (Long-Term) Cardiovascular Sequelae

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Abstract

Cardiovascular diseases (CVDs) and the coronavirus disease 2019 (COVID-19) pandemic represent major, interrelated global health challenges, largely mediated by dysregulation of the renin–angiotensin–aldosterone system (RAAS). Traditionally, therapeutic strategies have focused on inhibiting the classical ACE/angiotensin II (Ang II)/AT_1 receptor axis, which drives vasoconstriction, inflammation, fibrosis, and cardiovascular remodeling. However, the discovery of angiotensin-converting enzyme 2 (ACE2) has revealed an alternative, counter-regulatory RAAS pathway with significant physiological and therapeutic relevance, particularly in the context of COVID-19. ACE2 catalyzes the conversion of Ang II to angiotensin-(1–7), thereby activating the Mas receptor axis, which exerts vasodilatory, anti-inflammatory, antifibrotic, and antioxidative effects. SARS-CoV-2-induced downregulation of ACE2 disrupts this protective pathway, contributing to cardiovascular injury and post-COVID-19 complications. This review examines classical and alternative RAAS signaling, elucidates the molecular basis of ACE2-mediated cardioprotection, and critically evaluates emerging therapeutic strategies, including natural products targeting the ACE2/angiotensin-(1–7)/Mas receptor axis in cardiovascular disease and post-COVID-19 complications.

Keywords: *angiotensin-converting enzyme 2 (ACE2); renin–angiotensin–aldosterone system; angiotensin II; angiotensin-(1–7); cardiovascular disease; post-COVID-19 complications*

Citation: Eluwole OA, Ogunlade O. Targeting ACE2 in the Renin–Angiotensin–Aldosterone System: Post-COVID (Long-Term) Cardiovascular Sequelae. *Journal of Experimental Pharmacology and Toxicology* 2026;2. https://doi.org/10.64253/042026jept002

1. Introduction

Cardiovascular diseases (CVDs) remain a major global health burden and are a leading cause of morbidity and mortality worldwide. Their impact is particularly pronounced among populations of African ancestry, who experience a disproportionate burden of hypertension, stroke, and heart failure, often at younger ages [1, 2]. The COVID-19 pandemic has short- and long-term impacts on the cardiovascular system [3]; thus, it poses a double tragedy for vascular pathogenesis.

Renin–angiotensin–aldosterone system (RAAS) modulation involves the conversion of angiotensin I (inactive) by angiotensin-converting enzyme (ACE) to angiotensin II (Ang II), a potent vasoconstrictor, stimulating aldosterone release, increasing blood pressure, and promoting inflammation and fibrosis in the heart and vessels [3]. Upregulated ACE contributes to high blood pressure by boosting Ang II levels, leading to poor blood pressure control. Elevated Ang II via ACE promotes cardiac hypertrophy and fibrosis, resulting in heart failure and ischemic heart disease [3, 4].

In 2020, the global focus transitioned from non-communicable diseases, such as hypertension and coronary artery disease, to the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has been shown to exert significant detrimental effects on both the respiratory and cardiovascular systems [3, 4]. The interaction between SARS-CoV-2 and the RAAS has been a subject of intense investigation and debate. Initial concerns suggested that ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) might increase ACE2 expression and thereby facilitate viral entry. However, this hypothesis was largely theoretical and not supported by robust clinical evidence, leading to conflicting interpretations in early reports. Subsequent clinical studies and guideline

recommendations have largely supported the continued use of these medications, although some uncertainty remains regarding their differential effects across patient subgroups [5, 6].

The discovery of ACE2 over two decades ago distinctly explains the physiological and pathological functions of ACE via the alternative pathway in **Table 1** [7–9]. In the alternative RAAS pathway, classical RAAS activation is counterbalanced through ACE2-mediated conversion of Ang II to angiotensin-(1–7) [Ang-(1–7)], which activates the Mas receptor and, to a lesser extent, the AT_2 receptor (**Figure 1**). This signaling axis promotes vasodilation via enhanced nitric oxide bioavailability, natriuresis, anti-inflammatory responses, and inhibition of fibrosis and hypertrophy. Most importantly, ACE2 restrains renin–angiotensin-driven angiogenesis (RAAS overactivation) by modulating inflammatory and oxidative processes related to COVID-19, atherosclerosis, and stroke thrombosis pathogenesis [10, 11]. The comparative analysis of the two mechanistic ways is summarized in **Table 1**.

While substantial progress has been made in elucidating RAAS signaling pathways, several limitations remain. Much of the mechanistic evidence supporting ACE2-mediated cardioprotection is derived from experimental and animal studies, with limited large-scale clinical validation. Furthermore, variability in ACE2 expression across populations, disease states, and therapeutic exposures complicates translating these findings into clinical practice. Controversies also persist, particularly regarding the dual role of ACE2 as both a protective enzyme and a viral entry receptor for SARS-CoV-2, raising questions about whether upregulation of ACE2 is universally beneficial or context-dependent. Therefore, this review highlights the pathophysiology and physiology of RAAS pathways in the trend of cardiovascular and post-COVID-19 complications, thus suggesting therapeutic implications.

2. Methods

In this narrative review, we searched the published case reports, original papers and review articles across five databases (PubMed, ScienceDirect, Scopus, Google Scholar, and Web of Science) to understand the crosstalk between classical and alternative pathways of the renin–angiotensin–aldosterone system, the significance of ACE2 in the pathophysiological mechanisms of COVID-19 and cardiovascular implications, and the limitations of ACE inhibitors (ACEIs) and alternative therapy (natural products). The search spanned studies in the literature published in English from 2012 through January 2026, excluding the gray literature and non-peer-reviewed sources to uphold methodological rigor. This approach balanced comprehensiveness with scientific evidence, enabling critical evaluation of the review.

3. Classical Pathways of the Renin–Angiotensin–Aldosterone System

For decades, clinicians and researchers have focused on ACE due to its role in RAAS, specifically in the conversion of angiotensin I to angiotensin II, which acts via the AT1 receptor to promote vasoconstriction, cardiac hypertrophy, and sodium and water retention [12, 13].

In the classical RAAS pathway, renin, an enzyme secreted by the juxtaglomerular apparatus of the kidney, cleaves angiotensinogen, produced by the liver, to form angiotensin I. Angiotensin-converting enzyme (ACE), predominantly found in the lungs, further cleaves angiotensin I into angiotensin II (Ang II). Ang II acts as a potent vasoconstrictor and exerts pro-inflammatory and pro-thrombotic effects [13, 14]. Additionally, Ang II stimulates the release of aldosterone from the adrenal glands, leading to sodium and water retention. Collectively, this classical pathway contributes to increased peripheral vascular resistance, elevated stroke volume, and higher blood pressure.

4. Alternative Pathways and Resulting Therapeutic Potentials

Beyond the conventional RAAS mechanism, various studies investigated the interrelated inflammatory and oxidative mechanisms as hallmarks of cardiovascular disease pathogenesis [14, 15].

In the alternative pathway of the RAAS (**Figure 1**), angiotensin-converting enzyme 2 (ACE2), predominantly located in the lungs, converts angiotensin I to angiotensin 1–9. This intermediate peptide is subsequently converted to angiotensin 1–7 by the angiotensin-converting enzyme (ACE). ACE2 also plays a pivotal role in counteracting the harmful effects of Ang II within the RAAS. While Ang II is a potent vasoconstrictor that induces pro-inflammatory, pro-fibrotic, and hypertrophic responses, ACE2 mitigates these effects by converting Ang II into angiotensin-(1–7), a peptide known for its vasodilatory and anti-inflammatory properties [16]. This enzymatic conversion shifts the balance of RAAS toward a protective axis, opposing the detrimental effects of Ang II. ACE2 cleaves Ang II into angiotensin-(1–7), which then binds to the Mas receptor. The activation of this receptor triggers vasodilation, reduces fibrosis, and attenuates inflammation, directly opposing the harmful effects mediated by Ang II through the angiotensin II type 1 (AT1) receptor [15, 16]. By lowering Ang II levels and increasing angiotensin-(1–7), ACE2 helps maintain vascular homeostasis, reduce oxidative stress, and prevent tissue damage, thereby playing a protective role in the cardiovascular and renal systems. In the COVID-19

setting, the downregulation of ACE2 induced by SARS-CoV-2 may contribute to epicardial adipose tissue inflammation and ultimately to cardiac complications [17]. It is equally anticipated that, when SARS-CoV-2 infection increases the levels of Ang II and decreases the levels of Ang (1–7), a subsequent downregulation in the activity of the pyruvate dehydrogenase complex occurs. These findings highlight the essential role of ACE2 in modulating the RAAS and emphasize its therapeutic potential in diseases associated with elevated Ang II levels, such as hypertension and heart failure.

Angiotensin II elicits reactive oxygen species (ROS) production, increases the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), and upregulates vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells. The inhibitory activity of ACE2 reduces cellular hypertrophy by antagonizing AT1R activation, which subsequently decreases the phosphorylation of mitogen-activated protein kinases (MAPKs) via a reduction in NADPH oxidase 2 (NOX2) activity, thereby mitigating ROS formation [18, 19]. Unlike ACE, ACE2 reduces Ang II availability, thereby preventing the activation of pathways associated with cardiovascular disease progression [20].

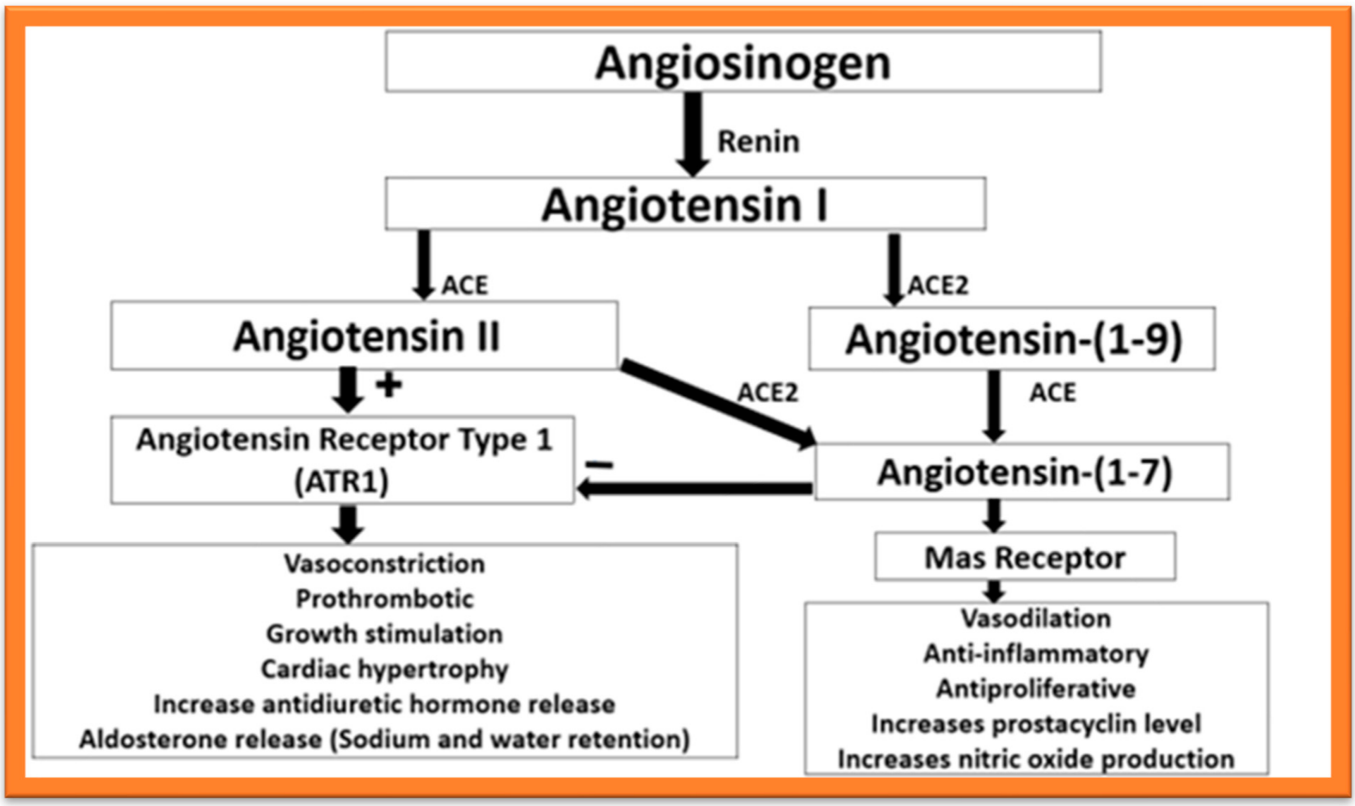

Figure 1. Classical and alternative pathways of renin–angiotensin–aldosterone activation.

Figure 1 shows the classical and alternative pathways of renin–angiotensin–aldosterone activation. Angiotensinogen is converted by renin to angiotensin I, which is metabolized through two opposing renin–angiotensin–aldosterone system pathways. In the classical pathway, angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II, activating AT_1 receptors and promoting vasoconstriction, and aldosterone release, and cardiac remodeling. In the alternative pathway, ACE2 converts angiotensin I or II to angiotensin-(1–7). Angiotensin-(1–7) acts via the Mas receptor to induce vasodilation, anti-inflammatory, and antiproliferative effects. Overall, the ACE2–angiotensin-(1–7)–Mas axis counterbalances the deleterious cardiovascular effects of the ACE–angiotensin II–AT_1 pathway.

Table 1. Summary of classical and alternative RAAS pathways.

Feature	Classical RAAS Pathway	Alternative RAAS Pathway
Primary trigger	Reduced renal perfusion, low sodium (Na^+), sympathetic activation	Counter-regulatory activation during RAAS overactivity
Initial enzyme	Renin	Renin
Key precursor	Angiotensinogen	Angiotensinogen
Major conversion enzymes	ACE (angiotensin-converting enzyme)	ACE2, neprilysin, prolyl endopeptidase
Main peptides	Converts angiotensin I to angiotensin II (Ang II)	Converts angiotensin I to Ang-(1–7) and Ang II to Ang-(1–7)
Principal receptors	AT_1 receptor (AT_1R)	Mas receptor (also AT_2 receptor, to a lesser extent)
Aldosterone involvement	Strong stimulation of aldosterone release	Inhibits aldosterone synthesis
Effects on blood vessels	Vasoconstriction	Vasodilation
Effects on sodium & water	Increased sodium and water reabsorption	Natriuresis and diuresis
Oxidative stress	Increased ROS production	Reduced oxidative stress
Inflammation	Pro-inflammatory	Anti-inflammatory
Fibrosis & remodeling	Promotes fibrosis and hypertrophy	Antifibrotic, anti-remodeling
Blood pressure outcome	Increases blood pressure	Lowers or normalizes blood pressure
Overall physiological role	Pressor, pathogenic when overactivated	Protective, counter-regulatory

RAAS—renin–angiotensin–aldosterone system; ACE2—angiotensin-converting enzyme; ROS—reactive oxygen species; AT_1—angiotensin II receptor type 1.

5. ACE2 Expression and COVID-19-Related Cardiovascular Complications

SARS-CoV-2 targets several ACE2-expressing tissues. The expression of ACE2 in different organs has been linked to their potential risk of SARS-CoV-2 infection. ACE2 expression occurs in body organs such as the lower respiratory tract, lung, heart, ileum, esophagus, kidney, and bladder [21]. Notably, the heart exhibits high ACE2 expression [18]. Studies highlight the direct and indirect impacts of SARS-CoV-2 on the CVS; these include heightened risks of acute cardiac injury, myocarditis, arrhythmia, and exacerbation of pre-existing cardiovascular conditions [3, 21]. Rare cardiovascular adverse events, including myocarditis and thrombotic complications, have been reported following COVID-19 vaccination; however, these events are uncommon and occur at substantially lower rates than cardiovascular complications associated with SARS-CoV-2 infection itself [22].

The mechanisms connecting SARS-CoV-2 infection to long-term cardiovascular consequences are deeply rooted in the dysregulation of the angiotensin-converting enzyme 2 (ACE2) system. Renin–angiotensin–aldosterone system (RAS) imbalance reduces ACE2, resulting in an accumulation of Ang II and a deficiency in Ang-(1–7). Unopposed Ang II acts on the AT1 receptor (AT1R), promoting inflammation, fibrosis, vasoconstriction, and oxidative stress, which drives long-term heart failure, ischemic heart disease, cardiomyopathy and vascular damage [23, 24].

ACE2 is highly expressed in pericytes and cardiomyocytes [25]. Virus-induced downregulation of ACE2 in these cells leads to capillary endothelial dysfunction, microvascular dysfunction, and persistent myocardial remodeling. Moreover, ACE2 also inactivates des-arginine bradykinin (DABK), a ligand that promotes inflammation via the B1 receptor. The loss of ACE2 leads to increased DABK/B1R signaling, which further increases vascular permeability and chronic inflammation [23, 25]. However, ACE2 deficiency leads to increased Ang II, which stimulates Plasminogen Activator Inhibitor 1 (PAI-1), the main inhibitor of fibrinolysis, leading to a pro-thrombotic environment and persistent hypercoagulable state, increasing the risk for stroke. Summarily, the long-term cardiovascular sequelae are not solely due to the acute viral infection but are driven by sustained dysregulation of the RAAS/ACE2 axis [25]. The initial downregulation of ACE2 sets off a prolonged state of tissue-level Ang II accumulation and reduced protective Ang-(1–7), resulting in chronic inflammation, microvascular dysfunction, and fibrosis. Notably, atrial fibrillation and ventricular tachycardia stemmed from electrolyte imbalances and chronic inflammation (IL-6 and TNF-α) [26–28].

The above-stated pathophysiological mechanisms of COVID-19 revealed the significance of ACE2 and the interaction between ACE inhibitors (ACEIs) and comorbidities. However, the context-dependent role of ACE2 in SARS-CoV-2 infection versus cardiovascular protection remains an important area of ongoing scientific debate. The underlying mech-

anisms linking vaccination to stroke are not fully elucidated, probably involving vaccine-induced immune thrombotic thrombocytopenia (VITT), molecular mimicry, and platelet activation pathways [27–29].

6. Mechanism of ACE2 Activation and Cues to Potential Therapeutic Agents

6.1. ACE2/Ang-(1-7)/MasR Axis Activity

Alterations in the renin–angiotensin–aldosterone system (RAAS) involving ACE2 lead to the modulation of angiotensin II (Ang II) and its conversion to angiotensin-(1-7) (Ang-(1-7), which exerts effects through the Mas receptor, promoting anti-inflammatory and antioxidative pathways, and contributing to systemic balance [29]. ACE2 metabolizes Ang II to Ang-(1-7), which exerts effects through the Mas receptor. ACE2 shedding at the membrane may lead to changes in Ang II levels, promoting Ang-(1-7)-mediated physiological and therapeutic effects, such as antifibrotic, antithrombotic, and vasodilatory properties [29, 30]. Excessive ACE2 shedding could diminish local tissue protection and exacerbate Ang II-mediated pathologies. However, Ang II production in response to oxidative stress may enhance ACE2/Ang-(1-7)/MasR axis activity, augment transcription of NF-κB, and release inflammatory cytokines [29, 31]. Viral binding causes ACE2 downregulation, internalization, and shedding from the cell membrane. ACE2 shedding produces soluble ACE2 (sACE2), which can act as a decoy; the primary effect is a loss of membrane-bound ACE2 leading to Ang II accumulation, which subsequently results in NF-κB activation [28–30]. The elevated Ang II binds to AT1R (angiotensin II type 1 receptor) on immune cells. This interaction directly activates the NF-κB signaling pathway, which triggers the nucleus to produce massive amounts of inflammatory cytokines (TNFα, IL-6, and IL-1β), leading to a cytokine storm [28, 29]. This pathological cascade is often mediated by ADAM17 (a disintegrin and metalloproteinase 17).

6.2. A Disintegrin and Metallopeptidase Domain 17 (ADAM17) Activity

Activation of the angiotensin II type 1 receptor (AT1R) by Ang II triggers a cascade of molecular events, including increased activity of ADAM17 (a disintegrin and metalloproteinase 17). ADAM17 facilitates the shedding of several membrane-bound proteins, such as ACE2 and tumor necrosis factor-α (TNF-α), releasing soluble TNF-α into the extracellular space, where it exerts auto- and paracrine effects [31]. This elevated ADAM17 activity contributes to reduced ACE2 levels on the cell surface, amplifying RAAS dysregulation and exacerbating cardiovascular conditions such as heart failure, atrial fibrillation, and coronary artery disease [32, 33]. ADAM17-mediated ACE2 shedding reduces membrane-bound ACE2, thereby amplifying Ang II–AT_1R signaling and worsening cardiovascular pathology.

6.3. Apelin and Its Analogs

Apelin, a bioactive peptide, has emerged as a cardioprotective molecule with a regulatory role in the expression of ACE2. ACE2 cleaves apelin peptides, including apelin-13 and apelin-36, through feedback mechanisms that influence cardiovascular homeostasis [34]. The persistent deficiency of apelin and APJ signaling is thought to contribute to unresolved inflammation, vascular dysfunction, and the long-term cardiovascular complications of post-COVID-19 exposure [35, 36]. Preclinical and clinical studies have demonstrated that apelin and its analogs counteract Ang II-mediated pathological changes, including oxidative stress, myocardial hypertrophy, and fibrosis, highlighting their potential as therapeutic targets [34–37]. The protective effects of apelin suggest that it and its agonists could be potential therapeutic candidates. Strategies targeting the apelin/APJ system, such as using stable apelin analogs or sodium–glucose cotransporter 2 (SGLT2) inhibitors that potentiate apelin–ACE2 signaling (e.g., dapagliflozin), are being investigated to mitigate cardiovascular and renal injuries associated with COVID-19 [38, 39].

7. Experimental ACE2 Therapeutic Targets

The interaction between SARS-CoV-2 and the RAAS has been a subject of intense investigation and debate. Initial concerns suggested that ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) might increase ACE2 expression and thereby facilitate viral entry [38, 39]. However, this hypothesis was largely theoretical and not supported by robust clinical evidence, leading to conflicting interpretations in early reports. Subsequent clinical studies and guideline recommendations have largely supported the continued use of these medications, although some uncertainty remains regarding their differential effects across patient subgroups.

Theoretically, ACE2 levels are increased following treatment with ACE inhibitors (ACEIs) and ARBs, which raises concerns that using these medications might increase the severity of COVID-19, especially in patients with existing cardiovascular diseases [39]. However, the experimental and clinical data showed conflicting results. A meta-analysis revealed that continuous administration of ACEI/ARB, compared with discontinuation, significantly reduced in-hospital mortal-

ity among patients with hypertension and COVID-19 infection. Meta-regression analyses indicated a clear association between the use of anti-hypertensive agents and reduced mortality in these patients [39, 40].

Studies have confirmed the potency of specific ACE2 inhibitors, such as MLN-4760, in research contexts to investigate ACE2 function; however, these inhibitors are not considered therapeutic agents for inflammatory diseases due to the protective role of ACE2 in mitigating inflammation [40, 41]. ACE2 activators, such as xanthenone and diminazene aceturate (DIZE), have been explored for their potential to enhance cardiac function and mitigate fibrosis through modulation of the renin–angiotensin system [9, 41]. Engineered probiotics expressing recombinant ACE2 proteins have shown promise in managing diabetic retinopathy [9]. Studies have also suggested that natural compounds capable of modulating ACE2 activity have potential as therapeutic agents [30] and may contribute to the mitigation of disease, and these may play a role in disease amelioration.

8. Future Perspectives

There are essentially no clinical data on how ACEIs or ARBs may impact the ACE2-Ang-(1–7) pathway in the lung, heart, or brain. Thus, additional data are urgently needed on the effects of ACEI and ARB on human pulmonary disease and RAAS expression, particularly the response of the ACE2–Ang-(1–7)–Mas receptor axis. Given the substantial disease prevention and therapeutic benefits of ACE2, researchers should explore the distinct effects of Mas receptor facilitators and their interrelationship with ACE2 expression on cardiovascular tissues. Polyphenol-rich plant extracts enhance ACE2 expression and Ang-(1–7) availability, while also facilitating Mas receptor signaling and suppressing aldosterone synthesis [32].

Notably, preclinical studies supporting phytochemical modulation of RAAS components are derived from in vitro and animal studies, with limited clinical trials validating efficacy and safety in humans. Variability in bioavailability, dosing, and phytochemical composition further complicates translation into therapeutic applications. Additionally, potential interactions with conventional RAAS-targeting drugs remain insufficiently explored, representing an important gap in the literature. **Table 2** and **Table 3** show the mechanistically linked table connecting the classical and alternative RAAS pathways to phytochemicals and medicinal plant extracts, with emphasis on ACE inhibition, ACE2 upregulation, AT_1 blockade, and Mas receptor activation. Polyphenols and flavonoids via the alternative ACE2–Ang-(1–7)–Mas receptor pathway promote vasodilation, reduce oxidative stress, inhibit aldosterone secretion, and restore endothelial function, thereby shifting RAAS signaling towards a cardioprotective phenotype. This review suggests amplification of the Mas receptor and study of its effects on ACE2 expression in the post-COVID-19 cardiac tissue.

Table 2. Linking RAAS pathways to phytochemicals and plant extracts.

RAAS Pathway/Target	Physiological Consequence	Key Phytochemicals	Representative Plant Sources	Mechanistic Relevance to Hypertension
Classical pathway (Ang II–AT_1R)	Vasoconstriction, sodium retention, oxidative stress	—	—	Pathological when overactivated
ACE inhibition	↓ Ang II formation	Flavonoids (quercetin, kaempferol), phenolic acids (caffeic, chlorogenic acid), peptides	*Allium sativum* (garlic), *Hibiscus sabdariffa*, *Camellia sinensis*, *Moringa oleifera*	Reduces Ang II-mediated vasoconstriction and aldosterone release
AT_1 receptor antagonism	↓Vasoconstriction, ↓ aldosterone	Terpenoids, saponins, alkaloids	*Azadirachta indica*, *Ocimum gratissimum*, *Panax ginseng*	Mimics ARB-like effects, limiting Ang II signaling
Renin inhibition	↓ Ang I formation	Polyphenols, bioactive peptides	*Camellia sinensis*, fermented legumes	Suppresses RAAS at its initiating step
Oxidative stress suppression (downstream of Ang II)	↓ ROS, ↓ inflammation	Flavonoids, carotenoids	*Curcuma longa*, *Zingiber officinale*, *C. ambrosioides*	Attenuates Ang II-induced endothelial dysfunction

RAAS—renin–angiotensin–aldosterone system; ACE2—angiotensin-converting enzyme; ROS—reactive oxygen species; Ang II—angiotensin II; ARB—angiotensin receptor blocker; AT1—angiotensin II receptor type 1. **Note:** Most evidence for phytochemical modulation of RAAS is derived from preclinical and observational studies. ↓- decreased.

Table 3. Alternative (protective) RAAS pathway.

RAAS Pathway/Target	Physiological Consequence	Key Phytochemicals	Representative Plant Sources	Mechanistic Relevance to Hypertension
ACE2 upregulation	Increased Ang-(1–7) formation	Polyphenols, flavonoids	*Resveratrol*-rich plants, *Camellia sinensis*, *Citrus* spp.	Shifts RAAS balance towards vasodilation
Ang-(1–7) enhancement	Vasodilation, natriuresis	Flavonoids, lignans	*Hibiscus sabdariffa*, *Ginkgo biloba*	Counteracts Ang II pressor effects
Mas receptor activation	NO release, antifibrotic action	Polyphenols, triterpenes	*Panax ginseng*, *Nigella sativa*	Promotes endothelial protection
AT_2 receptor stimulation	Vasorelaxation, anti-inflammation	Flavonoids	*Vitis vinifera*, *Cocoa*	Supports Ang II detoxification via AT_2 signaling
Aldosterone suppression	Reduced Na^+ retention, and fibrosis	Saponins, flavonoids	*Glycyrrhiza glabra*, *Moringa oleifera*	Reduces mineralocorticoid-driven hypertension

Reports of COVID-19-related strokes were documented in non-Africans, while in sub-Saharan Africa (SSA), there is a paucity of data due to poor reporting infrastructure and healthcare-seeking behaviors [11, 23]. However, a case report involving three patients in Tanzania has confirmed the link between COVID-19 and ischemic stroke [41]. Clinical trials of expressional inhibitors of ACE expression specifically among the population of high renin–angiotensin–aldosterone sensitivity are required for effective management of cardiovascular diseases and COVID-19 complications. Analysis of post-COVID-19 ACE2 expressions among people living with cardiovascular diseases will be beneficial in the effective management of cardiovascular disease. We advised that further investigation into these potential mechanisms is urgently required, given the current complex interplay of the RAAS and novel coronaviruses such as SARS-CoV-2. Particularly relevant information includes the status of the RAAS at baseline. In addition, studies focusing on ACE expression among COVID-19-vaccinated individuals and non-vaccinated individuals are recommended.

Future research should prioritize well-designed clinical trials to validate the therapeutic potential of ACE2-targeted strategies and phytochemicals in diverse populations. Addressing current gaps, including limited data from sub-Saharan Africa, inconsistencies in ACE2 expression profiles, and unresolved safety concerns, will be critical.

9. Conclusion

The complications of COVID-19 and cardiovascular diseases are strongly linked through dysregulation of the renin–angiotensin–aldosterone system. While the ACE2–angiotensin-(1–7)–Mas receptor axis represents a promising therapeutic target, current evidence is limited by a predominance of preclinical data and variability in clinical outcomes. Phytochemical interventions show potential in modulating RAAS balance; however, their clinical applicability remains uncertain due to insufficient human studies and standardization challenges. Importantly, the dual role of ACE2 in cardioprotection and viral entry continues to generate debate, underscoring the need for context-specific therapeutic approaches. Future studies integrating mechanistic, clinical, and population-based data will be essential to fully harness RAAS modulation in managing cardiovascular and post-COVID-19 complications.

Funding

This research received no external funding.

Author contributions

O.A.E. and O.O. jointly contributed to the conceptual design of the study. Methodological framework development was carried out by O.A.E. and O.O. The background literature was provided by O.A.E. The initial manuscript draft was written by O.A.E. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

Not applicable, as there was no original data assessed in the current publication.

Institutional review board statement

Not applicable, as there was no original data assessed in the current publication.

Informed consent statement

Not applicable, as there was no original data assessed in the current publication.

Additional information

Received: 2026-01-15
Accepted: 2026-05-13
Published: 2026-06-15

Publisher's note

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