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REVIEW

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Therapeutic targets of natural products for the management of cardiovascular symptoms of coronavirus disease 2019

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The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first occurred in China in December 2019 and subsequently spread all over the world with cardiovascular, renal, and pulmonary symptoms. Therefore, recognizing and treating the cardiovascular sign and symptoms that caused by coronavirus disease 2019 (COVID-19) can be effective in reducing patient mortality. To control the COVID-19-related cardiovascular symptoms, natural products are considered one of the promising choices as complementary medicine. Scientists are struggling to discover new antiviral agents specific to this virus. In this review, the natural products for management of cardiovascular symptoms of COVID-19 are categorized into three groups: (a) natural products with an impact on angiotensin II type 1 receptor; (b) natural products that inhibit angiotensin-converting enzyme activity; and (c) natural products that mimic adenosine activity. All these natural products should undergo clinical investigations to test their efficacy, safety, and toxicity in the treatment of cardiovascular symptoms of COVID-19. This article summarizes agents with potential efficacy against COVID-19-related cardiovascular symptoms.

KEYWORDS
ACE inhibitor, angiotensin II type 1 receptor, cardiovascular disease, COVID-19, mimic adenosine, natural products

1 | INTRODUCTION

Since the end of December 2019, a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Huang et al., 2020; Wu et al., 2020) that has affected countries around the world. Overall, coronavirus disease of 2019 (COVID-19) is an acute disease that can cause 2% mortality. Symptoms such as progressive respiratory failure and massive alveolar damage may be the cause of death in severe cases of the disease (Chan et al., 2020; Xu, Shi, et al., 2020). Preliminary efforts have concentrated on identifying, counting patients, and describing the clinical terms, and treating patients. The COVID-19 infection led to series of severe respiratory illness similar to severe acute respiratory syndrome coronavirus and was correlated with intensive care unit admission and high mortality (Huang et al., 2020). Additionally, the risk of death from COVID-19 may be higher in patients with cardiovascular disease (CVD) (Huang et al., 2020). Therefore, recognizing and treating the cardiovascular symptoms caused by coronavirus can be effective in managing this disease and decreasing the mortality rate. In this regard, natural products show a critical role as nutraceutical supplements and provide prospective health benefits in CVD. Compilation of data from epidemiological, experimental, and clinical trial studies point out that natural products have substantial cardioprotective impact in the prevention of CVD, therefore these are considered as cardiovascular-friendly natural products. At this point in time, there is an urgent need to cure and control all the symptom of SARS-CoV-2 infections, especially cardiovascular symptoms. In this review, the impact of natural product on managing the cardiovascular sequels of SARS-CoV-2 infections are highlighted.

2 | MECHANISM OF ENTRANCE OF COVID-19

The spike (S) protein in coronaviruses comforts the entry of viruses into target cells. This entry depends on the binding of the surface unit S1 of S protein of a cellular receptor that helps viral attachment to the surface of target cells. In addition, the entry requires S protein priming by cellular proteases, which entail S protein cleavage at the S1/S2 and the S2 site and allow fusion of viral and cellular membranes, a process driven by the S2 subunit (Hoffmann et al., 2020). SARS-S engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor (Li et al., 2003) via activation of the S protein by trans membrane protease serine 2 (TMPRSS2) (Clerkin et al., 2020). The expression of ACE2 mRNA is presented in human carotid atherosclerotic lesions. Furthermore, ACE2 protein is presented in nondiseased mammary arteries and atherosclerotic carotid arteries, human veins, endothelial cells, smooth muscle cells, macrophages (Sluimer et al., 2008), oral mucosa epithelial cells (Xu, Zhong, et al., 2020), and renal cells (Wu, et al., 2020). In order to investigate the infection caused by COVID-19 in human, organs such as lung, heart, esophagus, kidney, bladder, and ileum, as well as specific cells, particularly myocardial cells, type II alveolar cells, proximal tubule cells and bladder urothelial cells, esophagus and ileum epithelial cells are vulnerable for COVID-19 infection (Zou et al., 2020).

Since ACE2 is an important COVID-19 receptor, the binding of S protein of COVID-19 to ACE2 reduces its expression, and as a result, the ACE2 expression reduction causes acute respiratory failure (Kuba et al., 2005). The number of ACE2 is high in the heart, which is the result of angiotensin II in over activation of the renin-angiotensin system (RAS) in states like congestive heart failure, atherosclerosis, and hypertension (Tikellis & Thomas, 2012). In addition to the lung and heart, ACE2 is expressed in the vascular endothelium, kidneys, and the intestinal epithelium, leading to a mode of action to disrupt the function of several organs, causing COVID-19 infection (Tikellis & Thomas, 2012; Zhang, Penninger, Li, Zhong, & Slutsky, 2020). Evidence from clinical trials in patients with COVID-19 indicates that mortality from the disease is higher in people with CVD. Natural products are one of the most popular options for prevention, control, and treatment of the disease throughout the globe and widely grasped as an adjunct treatment to conventional therapy. Growing public awareness and scientific enthusiasm have conducted studies toward the importance of natural products in disease treatment and health promotion. On the other hand, natural products in the form of nutraceuticals ameliorate cardiovascular symptoms, as evidenced by various epidemiological, experimental and clinical trial studies (Shukla, Gupta, Ojha, & Sharma, 2010). Hence, in this review, we study the pharmacological activity of natural products for the management of cardiovascular symptoms of COVID-19.

3 | THE FUNCTION OF ACE, ACE 2, AND AT1 IN BALANCING CARDIOVASCULAR SYSTEM

ACE2 demonstrates the key role in the modulation of the RAS in health and disease, and essentially catalyzes the conversion of angiotensin II (Ang II) to Ang Hepapeptide-(1–7) (Vickers et al., 2002; Zisman, Meixell, Bristow, & Canver, 2003) that regulates Ang II activities and also forms in myocardial circulation and reduces when formation of Ang II is suppressed. The major generation of Ang-(1–7) in heart is depending on availability of Ang II. Ang II is a preference substrate for Ang-(1–7)-forming enzymes which shows a key role in the formation and regulation of Ang-(1–7). Formation of Ang-(1–9) is confirmed by ACE2, via hydrolyzation Ang I and also Ang-(1–7) from Ang II and selective ACE inhibitors do not inhibit these pathways. ACE2 demonstrates more affinity for Ang II hydrolysis compared to Ang I (Vickers et al., 2002). Moreover, in heart ventricular, ACE2-mediated virtually all Ang(1–7) formation from Ang II (Zisman, Keller, et al., 2003). The pathway is shown in Figure 1.

Ang II has a high affinity to two main types of receptors, namely, Ang II type 1 (AT1) and Ang II type 2 (AT2) receptors (Daviet et al., 1999; De Gasparo, Catt, Inagami, Wright, & Unger, 2000; Nouet et al., 2004). AT_2-receptor stimulation leads to antagonize the signaling in accordance with stimulation of AT_1-receptor. Since there is no difference between the binding affinity of Ang II for the AT_1 and AT_2 receptor, stimulation of AT_2-receptor demonstrates the same action of AT_1-receptor blockers (ARBs) (Dzau, 2005). The RAS and Ang II/AT1 receptor axis is shown in Figure 2.

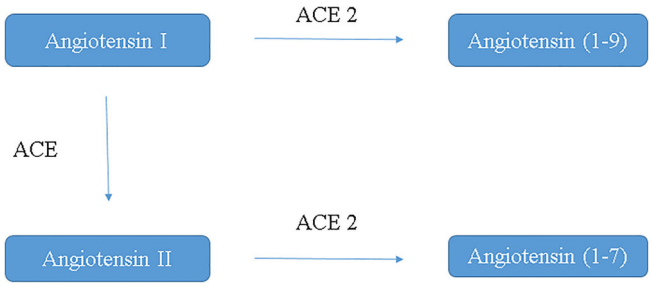

FIGURE 1 Angiotensin peptide pathway. ACE, angiotensin converting enzyme [Colour figure can be viewed at wileyonlinelibrary.com]

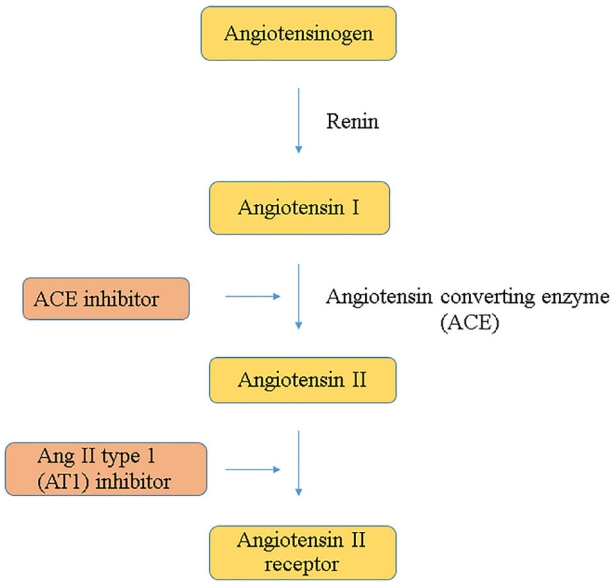

FIGURE 2 The RAS and Ang II/AT1 receptor axis [Colour figure can be viewed at wileyonlinelibrary.com]

However, the latest research shows that Ang-(1–7) has the most important activity in RAS. Ang-(1–7) causes vasodilation that antagonizes AT1-receptor stimulation-mediated vasoconstriction. These consequences reveal to be mediated by the bradykinin–nitric oxide pathway (Brosnihan, Li, & Ferrario, 1996; Ferrario, Chappell, Tallant, Brosnihan, & Diz, 1997). So, Ang-(1–7) results in reduction of blood pressure and exhibits an organ-protective activity such as cardioprotective activity in diabetic rats (Ebermann et al., 2008) and reduction of cardiac hypertrophy, fibrosis, and renal damage (Yamamoto et al., 2006). On the other hand, Ang-(1–7) potentiates bradykinin, through AT_2-receptor- or through ACE inhibitors (Gorelik, Carbini, & Scicli, 1998). Recent research on the function of ACE2 suggests that ACE2 has a main role in the severity of lung failure, for instance, in acute lung injury or in acute respiratory distress syndrome (ARDS) (Imai, Kuba, & Penninger, 2008). So, SARS-CoV-2 uses ACE2 as a key receptor for cell fusion and for in vivo infections, it seems that ACE2 is one of the etiological factors causing these pathological changes (Kuba, Imai, Rao, Jiang, & Penninger, 2006). In the ARDS pathogenesis, ACE upregulates Ang II and can cause severe lung failure through AT1 receptor (Imai et al., 2005). Besides, SARS-CoV-2 leads to ACE2 downregulation, which shows an important role in severe acute lung injury in SARS (Kuba et al., 2005). Finally, in acute lung injury, Ang II, ACE, and AT1 receptor function as lung-injury-promoting factors (Danilczyk, Eriksson, Oudit, & Penninger, 2004; Imai et al., 2005; Vickers et al., 2002). These outcomes illustrate not only ACE2 activity has a main function in CVD but it also causes damage or dysfunctions of other organs.

4 | NARURAL PRODUCTS WITH POTENTIAL PHARMACOLOGICAL EFFECTS IN CVD SYMPTOMS OF COVID-19

Disease treatment with natural products is getting popular all over the world and naturally occurring agents are widely used for complementary therapy of various ailments. Raising public knowledge and scientific attention have directed studies toward the function of natural products in health promotion and disease treatment. Natural products, including nutraceuticals, can have a great effect on the treatment of cardiovascular burdens of COVID-19, as evidenced by epidemiological, experimental and clinical studies (Shukla et al., 2010). In the following sections, the effects of natural products on AT1 receptors, ACE, and ACE2 and the compounds that mimic adenosine activity are discussed.

5 | NATURAL PRODUCTS THAT HAVE A DIRECT IMPACT ON AT_1 RECEPTOR

5.1 | The effect of plant products on AT_1 receptor

5.1.1 | *Guazuma ulmifolia*

Bioactive oligomeric and polymeric proanthocyanidins, which include (-) -epicatechin units, were isolated from the acetone extract of *Guazuma ulmifolia* Lam plant. These compounds were used to inhibit the binding of Ang II to the AT1 receptor (Table 1). Alteration of the [^{3}H]-Ang II binding was concentration-dependent and related to the degree of polymerization of various parts containing proanthocyanidins which are the most active material corresponding to the polymerized proanthocyanidins. The relation between Ang II and AT_1 receptor binding might be supposed as a potentially biological activity of proanthocyanidins provides the very broad-spectrum biological activities of the condensed tannins (Caballero-George et al., 2002). So it is possible that other highly polymerized proanthocyanidins or condensed tannins in plants, such as *Malus sylvester* (Guyot, Doco, Souquet, Moutounet, & Drilleau, 1997), brown soybean (Takahata, Ohnishi-Kameyama, Furuta, Takahashi, & Suda, 2001), horse chestnut (Kimura et al., 2011), and persimmon (S.-F. Xu, Zou, Yang, Yao, & Li, 2012) might be effective on blocking the AT1 receptors and need further investigations.

5.1.2 | Qiliqiangxin

Traditional Chinese drug qiliqiangxin, which has been developed via the meridian theory (W. Liu et al., 2012), can amend urine volume, cardiac function, and subjective symptoms in patients with chronic heart failure (Xiao, Song, Li, Liao, & Chen, 2009). Qiliqiangxin consists of 11 distinct combined herbs, including *Astragalus* sp. radix, ginseng radix and rhizome, *Descurainiae lepidii* semen, *Alismatis* sp. rhizome, *Polygonati odorati* rhizome, *Aconiti lateralis* radix preparata, *Salvia miltiorrhiza* radix and rhizome, *Cinnamomi ramulus*, carthami flos, periploca cortex, and *Citri reticulatae* pericarpium (Tao et al., 2015). Based on a study conducted by Duan et al. (2018), Western blot analysis showed that qiliqiangxin remarkably decreased the expressions of non-phagocytic cell oxidase 2, AngII, and B-cell lymphoma 2 (Bcl-2) associated X protein (Bax), and enhanced the expressions of ATR1 and Bcl-2 in the kidney. Qiliqiangxin remarkably decreased the level of apoptosis in kidney, which was induced by myocardial infarction. Altogether, qiliqiangxin might be a potentially efficient drug for the treatment of cardiorenal syndrome via regulating inflammatory/oxidative stress signaling. Considering these results, qiliqiangxin is an auspicious agent to treat the cardiac effects of COVID-19.

5.1.3 | *Carthamus tinctorius*

Carthamus tinctorius L., a member of the family Asteraceae, is widely used in folk medicine and as a beverage in Asian countries (Dajue & Mündel, 1996). The effects of *C. tinctorius* extract on vascular remodeling, hemodynamics, RAS, and oxidative stress on hypertensive rat model were studied by Dajue and Mündel (1996). This experiment showed that *C. tinctorius* extract suppressed activation of RAS, involving elevated ACE activity, Ang II level and upregulated expression of aortic AT_1 receptor protein. These findings suggest that *C. tinctorius* extract may involve in RAS inhibitory activity and have a potent antioxidant activity (Bunbupha et al., 2018). In general, such a study suggests the potential use of *C. tinctorius* in the prevention and treatment of cardiovascular and renal sequels of COVID-19.

TABLE 1 The pharmacological activity of natural products for the management of cardiovascular symptoms

Natural products	Mechanisms	Study types	References
Guazuma ulmifolia (Oligomeric and polymeric proanthocyanidins)	Inhibits the binding of Ang II to the AT1 receptor	Computational study	(Caballero-George et al., 2002)
Resveratrol	Suppresses the Ang II/AT1 receptor axis and increases the AT2 receptor/Ang 1–7/Mas receptor axis	In vivo (mouse model)	(Jang et al., 2018)
Ginsenoside Rb1	Attenuates myocardial fibrosis and cardiac hypertrophy and decreases the levels of β-myosin heavy chain, atrial natriuretic factor, collagen I, periostin, Ang II, ACE, and AT1 receptor	In vivo (rat model)	(Zheng et al., 2017)
Qiliqiangxin (Traditional Chinese drug contains 11 herbs)	Decreases the expressions of non-phagocytic cell oxidase 2, AngII, and Bax, and enhances the expressions of ATR1and Bcl-2 in the kidney	In vitro	(Duan et al., 2018)
Carthamus tinctorius L.	Suppresses activation of RAS, involving elevated ACE activity, Ang II level and upregulates expression of aortic AT_1 receptor protein	In vivo (rat model)	(Bunbupha et al., 2018)
Ocimum sanctum L.	Inhibits ACE in a concentration-dependent manner	In vitro	(Chaudhary, Nema, Maity, Bahadur, & Mukherjee, 2013)
Vitis vinifera (Flavan-3-ols)	Inhibits ACE	In vitro	(Fernández & Labra, 2013)
Moringa oleifera (Niazimin-A, niaziminin-B and niazicin-A)	Targets ACE via antihypertensive activity	Computational study	(Khan, Jaiswal, Kulshreshtha, & Khan, 2019
Peptide from hydrolysation of a peach seed	Inhibits ACE and reduces systolic blood pressure	In vivo (rat model)	(Vásquez-Villanueva, Orellana, Marina, & García, 2019)
Gelatin of milkfish	Inhibits ACE	In vitro	(Huang, Tsai, Hong, Hsieh, & Huang, 2018)
Camellia sinensis [purine alkaloids, main flavanols, (-)-epicatechin, (-) epigallocatechin, (-)-epicatechingallate and (-)-epigallocatechingallate]	Inhibits ACE concentration-dependently	In vitro	(Anesini, Ferraro, & Filip, 2008)
Fucus spiralis (Phlorotannins)	Inhibits ACE especially in patients with high blood pressure	In vitro	(Paiva, Lima, Neto, & Baptista, 2016)
Amphioctopus neglectus (Macrocyclic lactones)	Inhibits ACE and shows with anti-hypertensive activities along with scavenging potential radical- capacities	Ex vivo	(Chakraborty, Krishnan, & Joy, 2019)
Rheum officinale Baill, *Polygonum multiflorum* Thunb., and *Polygoni multiflorum* Thunb. (Anthraquinone and emodin)	Blocks S protein and ACE2 concentration-dependently	In vitro	(Ho, Wu, Chen, Li, & Hsiang, 2007)
Soybean (*Glycine max*)	Inhibits rhACE2	In vitro	(Takahashi, Yoshiya, Yoshizawa-Kumagaye, & Sugiyama, 2015)
Green tea (Japan), black tea (India) and Rooibos tea (South Africa)	Inhibits ACE with no substantial effect on NO	Randomized, three-phase, crossover study	(Persson, Persson, Hägg, & Andersson, 2010)
Huayu Tongluo herbs (Traditional Chinese drug radix and rhizome *Salviae Miltiorrhizae*, rhizome of Chuanxiong, Pheretima, Quanxie and Shuizhi)	Lowers urinary protein and promotes the ACE2-Ang-(1–7)-Mas axis, via upregulating the mRNA and enhancing protein expression of ACE2 and Mas	In vivo (rat model)	(J. Xu et al., 2014)

TABLE 1 (Continued)

Natural products	Mechanisms	Study types	References
Chinese yam	Ameliorates LPS-induced cardiac contractility via the deterrence of RAS and apoptosis possibly through an ER-SHC/RAS/Raf1-dependent mechanisms	In vitro and in vivo (rat model)	(Zeng et al., 2019)
1-Methylisoguanosine	Stimulates adenosine-sensitive adenylate cyclase, cardiovascular responses and skeletal muscle and function as a long-acting adenosine analogue	In vivo (mouse model)	(Baird-Lambert, Marwood, Davies, & Taylor, 1980)

Abbreviations: ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; Ang II, angiotensin II; AT1, angitensin II type 1 receptor; AT2, angitensin II type 2 receptor; Bcl-2, B-cell lymphoma; LPS, lipo-poly saccharide ; rh ACE2, Rhesus angiotensin converting enzyme 2.

5.2 | The effect of active compounds on AT_1 receptor

5.2.1 | Resveratrol

Jang et al. (2018) evaluated the effect of resveratrol for the RAS in aging kidneys. Eighteen mice were separated into two groups the placebo group and the resveratrol-treated group. Resveratrol-treated mice showed a better renal function and decreased albuminuria, with improved renal histological findings compared to a placebo group. The improvements included decreased in expression of collagen IV, nicotinamide adenine dinucleotide phosphate oxidase (NADP), 3-nitrotyrosine, 4,8-hydroxy-2′-deoxyguanosine, and fibronectin, whereas the expression of superoxide dismutase 2 and endothelial nitric oxide synthase was enhanced (Jang et al., 2018). Resveratrol also repressed the Ang II/AT1 receptor axis and increased the AT2 receptor/Ang 1–7/Mas receptor axis. These findings displayed that resveratrol shows preventative results on aging kidneys by decreasing oxidative stress, inflammation, and fibrosis, via Ang II suppression and Mas receptor activation (Jang et al., 2018). Altogether, resveratrol displayed suppression of Ang II/AT1 receptor axis through various mechanisms. This compound may represent a valuable candidate for the discovery and development of new antiviral drug to combat coronavirus infections.

5.2.2 | Ginsenoside Rb1

The ginsenoside Rb1 has been isolated from *Panax notoginseng* as one of the major active compounds (M. Liu & Zhang, 1995). This compound rehabilitated the cardiac cells in heart failure. H-ginsenoside Rb1 attenuated myocardial fibrosis, cardiac hypertrophy and also decreased the levels of β-myosin heavy chain, atrial natriuretic factor, collagen I, periostin, Ang II, ACE, and AT1 receptor. In addition, ginsenoside Rb1 might restitute cardiac/mitochondrial function via the Akt, extracellular-signal-regulated kinase (ERK), and transforming growth factor-β1 (TGF-β1)/Smad signaling pathways (Zheng et al., 2017). This indicates the possible application of ginsenoside Rb1 for COVID-19 infection-related cardiac effects.

6 | NATURAL PRODUCT THAT HAS A DIRECT ACE-INHIBITORY IMPACT

6.1 | *Ocimum sanctum*

Ocimum sanctum L. is used in several ancient systems of traditional medicine, such as Ayurveda, Greek, Roman, Siddha, and Unani (Gupta, Prakash, & Srivastava, 2002). In the study performed by Chaudhary et al. (2013), leaves, oil, and ethyl acetate fractions of *O. sanctum* as well as pure compound eugenol demonstrated ACE-inhibitory activity in a concentration-dependent manner. *O. sanctum* extract/fractions, oil, and eugenol inhibited ACE and exhibited antihypertensive action. Therefore, the authors concluded that *O. sanctum* may be useful in the inhibition of CVD-related to ACE activity and might have a prosperous future in the prevention and treatment of cardiovascular sequels of COVID-19.

6.2 | Grapes and wines

Several studies revealed the antiviral properties of grapes and wines (Bekhit et al., 2011; Konowalchuk & Speirs, 1976). Flavan-3-ols from red grape seeds and skin extracts with high proanthocyanidins showed ACE-inhibitory activities and raw seed and skin extracts inhibited over 80% of ACE activity. However, the purified seed and skin extracts lost their ability to inhibit ACE after intestinal digestion (Fernández & Labra, 2013). As an antiviral extract, grape extract can be considered as a source of antiviral compounds. The findings indicate that the inhibitory effect of red grape seed and skin extracts on ACE may have therapeutic potential and these extracts may be useful for the treatment of COVID-19-related CVDs.

6.3 | *Moringa oleifera*

In W. Liu et al. (2012) study, *Moringa oleifera* demonstrated an antiviral activity against a newcastle disease virus in ovo. Several isolated compounds from *M. oleifera*, namely niazimin-A, niaziminin-B, and niazicin-A, were reported to exhibit potent antihypertensive activities

through targeting ACE. According a study conducted by Khan et al. (2019), these molecules computationally have shown greater energy for better binding than standard drugs, which previously known for inhibition of ACE and can act as a great pharmacophore for in vitro and in vivo research in the development of potent drugs. Altogether, according to these results, isolated compounds from *M. oleifera* are good choices for evaluating the impacts of these natural compounds on the cardiovascular symptoms of COVID-19.

6.4 | Peach seed

A peptide fraction from hydrolyzed peach seed revealed high ACE-inhibitory activity. Vásquez-Villanueva et al. (2019) demonstrated that this peptide fraction containing isoleucine-tyrosine-serine-proline-histidine (IYSPH) showed the highest capacity for inhibition of ACE. Cytotoxic effects of peptides were demonstrated in three different cell lines, namely HeLa, HT-29, and HK-2. Oral administration of peach seed peptide fraction or peptide IYSPH led to a remarkable systolic blood pressure reduction in spontaneously hypertensive rats. The systolic blood pressure reduction and ACE-inhibitory properties of peach seed peptide fraction may increase the host's defense against COVID-19 infection. However, the underlying mechanisms are not clear and require future evaluation.

6.5 | Fish gelatin

Huang et al. (2018) isolated fish gelatin from nonextruded milkfish scale and extrusion-pretreated milkfish scale. The extracted gelatins were hydrolyzed to yield four different hydrolysates. In addition, these hydrolysates showed ACE-inhibitory activities (Huang et al., 2018). Further research is needed to explore the safety and efficacy of this natural supplement in food and nutraceutical products in controlling the cardiovascular symptoms of coronavirus.

6.6 | *Camellia sinensis*

Camellia sinensis exhibits various pharmacological effects on the cardiovascular system, including antioxidative (Anesini et al., 2008), antiproliferative (Santos et al., 2018), anti-angiogenic (Rashidi, Malekzadeh, Goodarzi, Masoudifar, & Mirzaei, 2017), and nitric oxide (NO) synthase-activating properties (Siamwala et al., 2013). In a study executed by Persson, Josefsson, Persson, and Andersson (2006), purine alkaloids and main flavanols present in green and black tea were evaluated for their effects on ACE and NO in human umbilical veins cultured endothelial cells. According to the results, a concentration-dependent and significant inhibition of ACE activity was observed for both green and black tea. In addition, (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechingallate, and (-)-epigallocatechingallate inhibited the ACE concentration dependently. In conclusion, tea extracts from *C. sinensis* may have the potential effect to prevent and protect against CVD and may increase the host's defense against coronavirus infection; however, the scientific confirmation is lacking.

6.7 | *Fucus spiralis*

Recently, algae have received much attention as a natural source of ACE inhibitors, such as the phlorotannins that are principal polyphenols in brown algae (Wijesekara & Kim, 2010). The study of Paiva et al. (2016) reports ACE inhibition by brown algae *Fucus spiralis*. Studies have shown that *F. spiralis* can be a potent source of ACE inhibitors with a great effect on public health, especially in patients with high blood pressure and can also be useful for cardiovascular effects of COVID-19 infection.

6.8 | Amphioctopus neglectus

Amphioctopus neglectus (family: Octopodidae) is known as a delicious seafood in many cultures, especially in the Mediterranean and Asian coasts. Macrocyclic lactones isolated from *A. neglectus* demonstrated potential radical-scavenging property and antihypertensive activity via inhibiting ACE. Chakraborty et al. (2019) showed the protective effect of the separated macrocyclic lactones was mediated by augmentation of antioxidant systems, which subsequently reduced the hypertension-related disorders. So, in viral infections like COVID-19, promising effects may be expected from *A. neglectus* through inhibition of ACE.

7 | NATURAL PRODUCTS WITH A DIRECT ACE-2-INHIBITORY IMPACT

7.1 | Polygonaceae family

Three Chinese medicinal plants from the Polygonaceae family inhibited S protein of COVID-19 and ACE2. The half-maximal inhibitory concentration (IC_{50}) value for *Rheum officinale* Baill. root tubers, *Polygonum multiflorum* Thunb., and the root tubers, caulis and vines of *P. multiflorum*, ranged from 1 to 10 μ/ml. Based on a study by Ho et al. (2007), anthraquinone and emodin, two compounds isolated from genus Rheum and Polygonum, remarkably blocked the S protein and ACE2 interaction in a concentration-dependent manner. These findings suggest that emodin could be considered as a potential lead therapeutic agent for the treatment of COVID-19 infection.

7.2 | Soybean

According to a study conducted by Takahashi et al. (2015), soybean (*Glycine max*) showed rhACE2 inhibitory effect. Based on results of Takahashi et al., the active ingredients of *G. max* that identified as ACE2iSB, strongly inhibited rhACE2 activity with an IC_{50} value of 84 nM (Takahashi et al., 2015). Hence, *G. max* can be used as

nutraceuticals for managing the cardiovascular sequels of coronavirus infection; however, further clinical investigations are warranted.

7.3 | *Camellia sinensis*, *Camellia sinensis var. assamica*, and *Aspalathus linearis*

Persson et al. (2010) investigated the effects of *Camellia sinensis* (green tea), *Camellia sinensis var. assamica* (black tea), and *Aspalathus linearis* (Rooibos tea) in reducing the patients' mortality from CVD. Additionally, the effect of three different kinds of tea, such as green tea (Japanese Sencha), black tea (India Assam Broken Orange Pekoe), and Rooibos tea (South Africa) have been investigated on the ACE and NO in a randomized, three-phase, crossover study. According to the results, oral administration of one dose of Rooibos tea and green tea remarkably inhibited ACE activity 60 min after administration of the tea. Although, no substantial effect on NO concentration was observed. These results offer that green tea and Rooibos tea with ACE inhibitory activity revealed cardiovascular protective activity (Persson et al., 2010) and also might cover the cardiovascular symptoms of COVID-19, which needs further evaluation.

7.4 | Huayu Tongluo herbs

Evaluating the effect of Huayu Tongluo herbs, which is consisted of the combination of radix and rhizome of *Salviae Miltiorrhizae*, rhizome of Chuanxiong, Pheretima, Quanxie (Scorpio), and Shuizhi (Hirudo) (Pan, Chen, Ma, Guo, & Jia, 2013) on ACE-2 -Ang-(1–7)-Mas axis, has demonstrated renal protection in diabetic nephropathic rats. According the study of J. Xu et al. (2014), these Chinese herbs lowered urinary protein and promoted the ACE2-Ang-(1–7)-Mas axis via upregulating the mRNA and enhancing protein expression of ACE2 and Mas. Therefore, the results encourage the use of these Chinese herbs for the treatment of viral diseases like COVID-19.

8 | NATURAL PRODUCTS THAT MIMICS ADENOSINE ACTIVITY

The remdesivir (1′-cyano-substituted adenosine nucleotide), is a prodrug that is derived from nucleotide (Agostini et al., 2018), exhibited broad-spectrum antiviral activity against plenty of RNA viruses in particular coronavirus via blocking RNA-dependent RNA polymerase (Tchesnokov, Feng, Porter, & Götte, 2019). These classes of compounds may have therapeutic impact on COVID-19. Therefore, the natural products that mimic adenosine activity or having the similar structure are discussed in following section.

8.1 | Chinese yam

Zeng et al. (2019) carried out the study to evaluate the impact of Chinese yam extract and adenosine on lipopolysaccharide (LPS)-induced cardiac anomalies and associated mechanism of action. Based on results, the Chinese yam extract and adenosine led to amelioration of heart function, downregulation of proinflammatory cytokines, suppression of RAS and mitogen-activated protein kinases (MAPK), inhibition of apoptosis markers, and elevation of estrogen receptor (ER) and SHC/Ras/Raf1 expression. Finally, it was evident that Chinese yam extract along with adenosin improved LPS-induced cardiac contractility via inhibition of RAS and apoptosis possibly through an ER–SHC/Ras/Raf1-dependent mechanism (Zeng et al., 2019). In summary, Chinese yam extract in conjunction with adenosin may be effective to treat cardiovascular ailments of viral diseases like COVID-19.

8.2 | 1-Methylisoguanosine

1-Methylisoguanosine, a marine secondary metabolite, is isolated from marine sponge *Tedania digitate*. It has skeletal muscle relaxant, cardioprotective, and hypothermic effects. The cardioprotective effects of this compound are similar to those of adenosine. A series of 1-methylisoguanosine analogs has been evaluated through structure-activity studies, and it has been suggested that there is a direct connection between the compounds' ability to stimulate adenosine-sensitive adenylate cyclase and cardiovascular responses and skeletal muscular effects. Thus, it appears that 1-methylisoguanosine may function as a long-acting adenosine analog (Baird-Lambert et al., 1980). Finally, due to the importance of pure compounds in combating coronavirus, 1-Methylisoguanosine could pave the road for identifying novel antiviral agent for the treatment of SARS-CoV-2infection.

9 | CONCLUSIONS AND FUTURE DIRECTION

Natural compounds can demonstrate a synergy along with pharmacological treatments in several kinds of pathologies (Di Lodovico et al., 2019). Due to the prevalence of COVID-19 disease, there is an instant quest for safe, efficient, and relatively low-cost new drug candidates. Evidence from in vitro and in vivo studies suggests that the medicinal plants and natural products discussed in this review significantly modified various molecular, cellular, and metabolic mechanisms that control both cardiovascular pathogenesis and COVID-19-related cardiovascular symptoms. In this review, the medicinal value of natural products on CVDs and COVID-19 has been presented in Table 1 and summarized in Figure 3. Emerging evidence clearly demonstrates that these herbal medicines have strong therapeutic properties and can improve pathological conditions related to CVDs and coronavirus-inflicted cardiovascular symptoms. However, proven clinical therapeutic benefits of these natural agents have not yet been realized yet. Hence, treatment using these natural agents cannot be initiated without further studies. Further, the safety and toxicity of various natural products have not been established. We conclude that well-designed preclinical studies and clinical trials involving larger sample sizes are

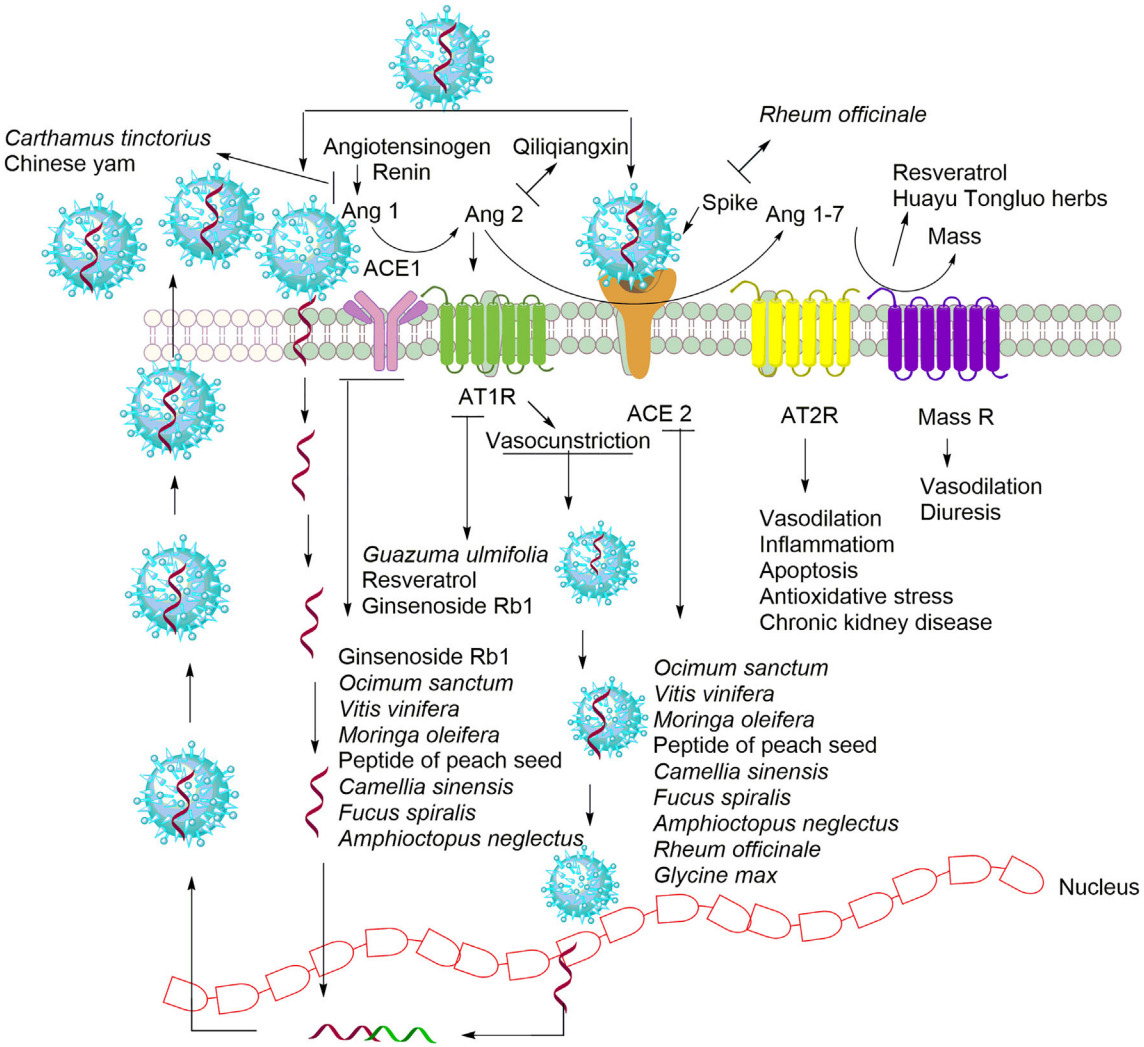

FIGURE 3 COVID-19-related cardiovascular anomalies and the effects of natural products to counteract these adverse effects. ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; Ang II, angiotensin II; AT1, angitensin II type 1 receptor; AT2, angitensin II type 2 receptor [Colour figure can be viewed at wileyonlinelibrary.com]

needed to investigate the role of different natural products and their underlying mechanisms in the context of COVID-19-related CVDs. Furthermore, the safety and toxicity of these natural products should be evaluated by future clinical trials.

CONFLICT OF INTEREST

The authors have no other conflicting interests to disclose.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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