



## REVIEW ARTICLE

## A HERBAL APPROACH AND MOLECULAR MECHANISMS OF PATHOGENESIS ASSOCIATED WITH CARDIOVASCULAR DISEASE IN SARS-COV-2 INFECTION

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### Abstract

A global public health emergency emerges as coronavirus disease COVID-19 is caused by a novel corona virus recognized as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Comorbidity is identified as a major health risk factor in people with COVID-19 infection and leads to a remarkable and sudden increase in the mortality rate worldwide. Despite the age-related factor, comorbidities are a major concern for intervention in patients with COVID-19 infection. Comorbidities with increased risk of mortality are mainly associated with diseases like cardiovascular, respiratory, cancer, and diabetes. The most prevalent complications are associated with cardiovascular diseases, which mainly include heart failure, cardiac arrhythmia, cardiac injury, hypertension, myocarditis, and disseminated intravascular coagulation (DIC). The present review highlighted the underline molecular mechanism involved in the pathogenesis of different diseases of the cardiovascular system. After invading to host cell SARS-CoV-2 opted for different molecular pathways for pathogenesis which mainly includes renin-angiotensin-aldosterone system (RAAS) through the use of ACE2 receptor specificity, cardiac injury with (cTnI and NT-pro BNP) proteins, coagulation (D-dimer), and involvement of complex networking of cytokine skeletons with interleukin (IL-6, IL-7, IL-22, IL-17). Meanwhile, people claim that COVID-19 can be avoided or even reversed by consuming herbal immunomodulators. But, specific preclinical and clinical trials have not been performed to test the efficacy.

**Keywords:** COVID-19; cardiovascular diseases; severe acute respiratory syndrome coronavirus 2, herbal medicine

### Introduction

In early December 2019 in Wuhan provenance of China firstly reported cases of the novel coronavirus infectious disease (COVID-19) which is identified later to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and subsequently very rapidly spread globally and emerges the biggest pandemic in the history of mankind (over 48,000,000 confirmed cases as on 05/11/2020) (Badawi & Ryoo 2016). Given finding the genetic identity, sequencing analysis followed by methodological purification of bronchoalveolar lavage fluid samples of, SARS-CoV-2 is revealed close relation to two bat-associated SARS-like coronaviruses (approximately 70 % identity) and similarly, approximately 50 % identity for the Middle East respiratory syndrome (MERS)-CoV (bavishi *et al.*, 2020). After the first reported case in China, WHO declared the COVID-19 outbreak had become a pandemic on 30 January 2020. A high mortality rate and rapidly increasing the infection of COVID-19 cases over time make it more challenging to control the disease spread. As of date, no promising anti virals and vaccines have been approved for SARS-CoV-2.

### Cardiovascular abnormalities in SARS-CoV-2 infection

A close correlation between CVS diseases and SARS have postulated in previously reported studies, that highlighted patient infected with SARS-CoV-2 had suffered from different CVS complications mainly includes, 71.9% of tachycardia, 50.4% of hypotension, 14.9% of bradycardia, and 10.7% of reversible cardiomegaly (Bonow *et al.*, 2020). In another set of Meta-analysis on 637 cases of MERS revealed a high incidence of hypertension i.e. approximately

50% of total cases and in 30% of cases, it was observed that heart diseases (Chaoman *et al.*, 2020). COVID-19 infection shows a distinct aspect of pathogenesis and CVS complications as compared to SARS and MERS (Chen *et al.*, 2020; Clerkin *et al.*, 2020).

### Molecular Mechanisms of SARS-CoV-2 infection

Pathogenesis of COVID-19 infection follows a complex molecular mechanism with a clinical presentation of different symptoms such as respiratory distress, flu, multiple organ failure, and eventually, the occurrence of deaths (Table 1). Previously reported studies highlighted the complex molecular step in support of the interaction that made between SARS-CoV-2, and ACE2 receptor (Coutard *et al.*, 2020; Danser *et al.*, 2020). Viable Epithelial cells of lungs expressed predominantly with type 1 membrane-bound ACE2 receptors (Ferrario *et al.*, 2005). When made a comparison between the SARS-CoV-2 and viruses responsible for the pathogenesis of SARS based upon the binding affinity to that of ACE2 receptor SARS-CoV-2 utilizes spike glycoprotein belong to a precise amino acid for binding despite from the other viruses (Figure 1). Noticeably, the S1 domain of the spike glycoprotein S recognition for the host cell between SARS-CoV and SARS-CoV-2 had a remarkable difference, which was identified to be higher affinity in SARS-CoV-2 (~55%) (Gallagher *et al.*, 2012). The receptor-binding domain (RBD) was identified as the most significant contributing domain for interaction between SARS-CoV-2 and ACE2 receptor (Gallagher *et al.*, 2012). The increased affinity of the virus is correlated to a preliminary mutation in RBD, along with furin makeover at

the cleavage site of the membrane, followed by another set of mutations in S1/S2 subunits of the spike S-protein (Guan *et al.*, 2020). Initial, cleavage of membrane-bound ACE2 protein is made with the help of two proteins which is up regulated by the process of endocytosis of SARS-CoV-2 spike S proteins which mainly includes A Disintegrin and Metalloproteases 17 (ADAM17). Furthermore, on the cell surface where ACE2 contains an enzymatic domain responsible for the conversion of Ang II (1–9) to Ang 1–7 (Huang *et al.*, 2020). This led to the down regulation of ACE2 and negative regulation RAAS system, which carried out by SARS-CoV-2, resulted in the formation of cytokine storm inside the cell and overall resulting in exaggerated inflammatory response intracellular changes. Figure 1, At last, structure-activity relationship-based affinity and interaction of SARS-CoV-2 to either ACE2 or the S protein postulated the significance of binding site recognition in COVID-19 infection. This information may be useful insights to focus a prospective for targeting against COVID-19 infection.

### **Involvement of ACE2 in cardiovascular complications**

Despite some promising case report studies possible implication to myocarditis in case of SARS-CoV-2 infection is still not properly documented (Inciardi *et al.*, 2020). According to the earlier reported data on the patients from Wuhan provenance postulated that 25% of hospitalized and treated patients had CVD complications (Keidar *et al.*, 2007). A separate group of studies explores the initial role of ACE2 in the pathogenesis of COVID-19 infection (Kwong *et al.*, 2018). Despite, ACE2 had identified to be localized in different tissues of the cardiovascular system mainly include vascular smooth cells, cardiomyocytes, vascular endothelium cardiac fibroblasts, and pericytes (Lan *et al.*, 2020). The direct proliferation of SARS-CoV-2 in the heart is still a topic for discussion. Pre-existing CVD comorbidity in the case of COVID-19 patients shows worsen outcomes (Lang *et al.*, 2020). As very, less reported pathological studies conducted on the COVID-19 patients. 12% of reported cases of SARS-CoV-2 include pathological features such as acute cardiac injury +. Based on previously reported clinical data postulated COVID-19 patients had hypertension (15% to 30%) and coronary heart disease (2.5% to 15%) (Lingouri *et al.*, 1996). The most common mechanisms responsible for the pathogenesis of cardiac injury highlighted the role of viral involvement for the systemic inflammation of cardiomyocytes + Thus, revealed the possible role of inflammation in the pathogenesis of myocardial injury (Lippi *et al.*, 2020). Previously reported Experiments suggested a molecular involvement of ACE2 in cardiovascular function.

### **SARS-CoV-2 induced cardiovascular damage**

A COVID-19 patient had increased troponin release (Lippi *et al.*, 2020) and can develop heart failure, cardiac arrhythmias, pericarditis, myocarditis, and vasculitis. The increased affinity for a binding site for (ACE2) receptor in vascular endothelial and lung tissue had shown by the binding specific structure of SARS-CoV-2 (Liu *et al.*, 2020). Patients with cardiovascular diseases will be considered as a

high-risk group as they having a higher risk to develop respiratory virus illness (Liu *et al.*, 2002; Lu *et al.*, 2020). Increase risk for myocardial injury and inflammatory response made through ACE2 receptor to myocardium and artery vessels through by SARS-CoV-2 virus (Roca *et al.*, 2017). ACE2 expression is down regulated on the other side ACE2 functions may be up regulated in case of heart failure (Sagar *et al.*, 2012), indicating a remarkable increase in the activity of ACE2. Relevantly, immune modulation by interacting with macrophages in the setting of inflammation is also exerted by ACE2 (Shang *et al.*, 2020), and previously reported studies also explore the role of ACE2 in reducing the levels of angiotensin II which is considered to cause pro-inflammatory and pro-oxidant, effects (Song *et al.*, 2018; South *et al.*, 2020).

### **SARS-CoV-2 and hypertension**

The relationship of COVID-19 with hypertension is linked through the role of ACE2. The Renin-angiotensin-aldosterone system (RAAS) utilizes ACE2 as a vital element in governing the pathogenesis of hypertension (Sun *et al.*, 2020). Previous experimental protocol revealed that the implication of angiotensin II receptor blockers (ARBs) or ACE inhibitors (ACEIs) resulted in a remarkable elevation of ACE2 tissue levels (Tang *et al.*, 2020; Thomas *et al.*, 2010). It also postulated that RAAS inhibitors in experimental models exert protective influence (Uri *et al.*, 2014). Hypertension is a contributing risk factor for been susceptible to infection of SARS CoV- 2 is still unclear the previously reported studies indicate the prevalence rates of 15–40%, whereas, the rates of high blood pressure in the general population (30%). For an instant, in case of most serious disease case hypertension observed to be is more prevalent in patients. One of the reported studies in China highlighted that in the case of non-severe disease cases prevalence of hypertension was found to be 13.4% of subjects whereas, in case of severe disease condition it was 23.7 %.

### **SARS-CoV-2 and cardiac arrhythmia**

Cardiac arrhythmia molecular pathology involved activation of the sympathetic nervous system, metabolic dysfunction, and myocardial inflammation, and, all of the above associated with viral infections. A previously reported study on 138 hospitalized COVID-19 patients, postulated that patients develop arrhythmias was 16.7% which emerges as the second most serious complication among others. In non-ICU patient, it was 7 % whereas in ICU patient it was 44%.

### **SARS-CoV-2 and heart failure and myocardial injury**

Recent studies revealed that there is remarkably elevated levels of lactate dehydrogenase (LDH) and serum creatinine kinase (CK) among the COVID-19 patients who required hospitalization (Veduganathan *et al.*, 2020; Varga *et al.*, 2020; Wang *et al.*, 2020) Besides, it is also reported that in case of SARS-CoV-2 infection fulminant myocarditis is prominent cardiac complications with potential outcomes. One of the reported studies in China, explore that 23 % of a hospitalized patient was to develop heart failure as a severe complication, with 52 % cases among non-survivors as

compared with 12 % of survivors (Wang *et al.*, 2020). In another study protocol in Wuhan suggest that a remarkable elevation of high-sensitivity cardiac troponin I (cTnI) (>28 pg/mL) in myocardial injury in case 5 of the first 41 patients [35, 36, 37]. In another set of study in Wuhan provenance for fetal cases (68), 53 % i.e.36 patients died because of respiratory failure, 7%, i.e. five patients dies because of myocardial damage, and 33% i.e. 22 patients died because of both common pathogenesis (Wu *et al.*, 2020)

### SARS-CoV-2 and myocarditis

A recent report of the National Health Commission indicates mononuclear cell infiltrates and myocyte necrosis as a contributing factor for cardiac injury and acute myocarditis as a result of acute viral infection complications. The acute cause of cardiac injury was identified as fulminant myocarditis in a patient with COVID-19 infection<sup>38, 39</sup>. But still clinical and molecular involvement become an area of research (yan *et al.*, 2020). To detect the presence and severity of myocardial infarction changes in transient ECG will be a significant tool along with other diagnostic tools includes cardiac MRI for the screening of myocardial infarction<sup>41</sup>. One of the reported Biopsy, a study in Europe on patients with acute myocarditis postulated that ranges of viral etiology between 37.8 % and 77.4 % (Yu *et al.*, 2006; Zheng *et al.*, 2020; Zhou *et al.*, 2020).

### SARS-CoV-2 and coagulation dysfunction

In COVID-19, the patient prevalence of pulmonary embolism and disseminated intravascular coagulation (DIC) with a remarkable elevation of fibrin degradation products and D-dimer levels are observed. One of the reported studies indicated an observed level of DIC in 71.4% of non-survivors (Zhou *et al.*, 2020). Along with significant elevation of pulmonary embolism (Zheng *et al.*, 2020; Zhou *et al.*, 2020). In a retrospective cohort study, from China evaluated the increased levels of D-dimer in COVID-19, patients as one of the adverse outcomes where D-dimer levels (>1 g/L) was associated with mortality in hospitalized patient.

### Use of herbal drugs to treat COVID-19

In this scenario, where preventive and therapeutic agents have not been developed and are prescribed for patient administration, many individuals in the community commonly use herbal medicines. A molecular function of the

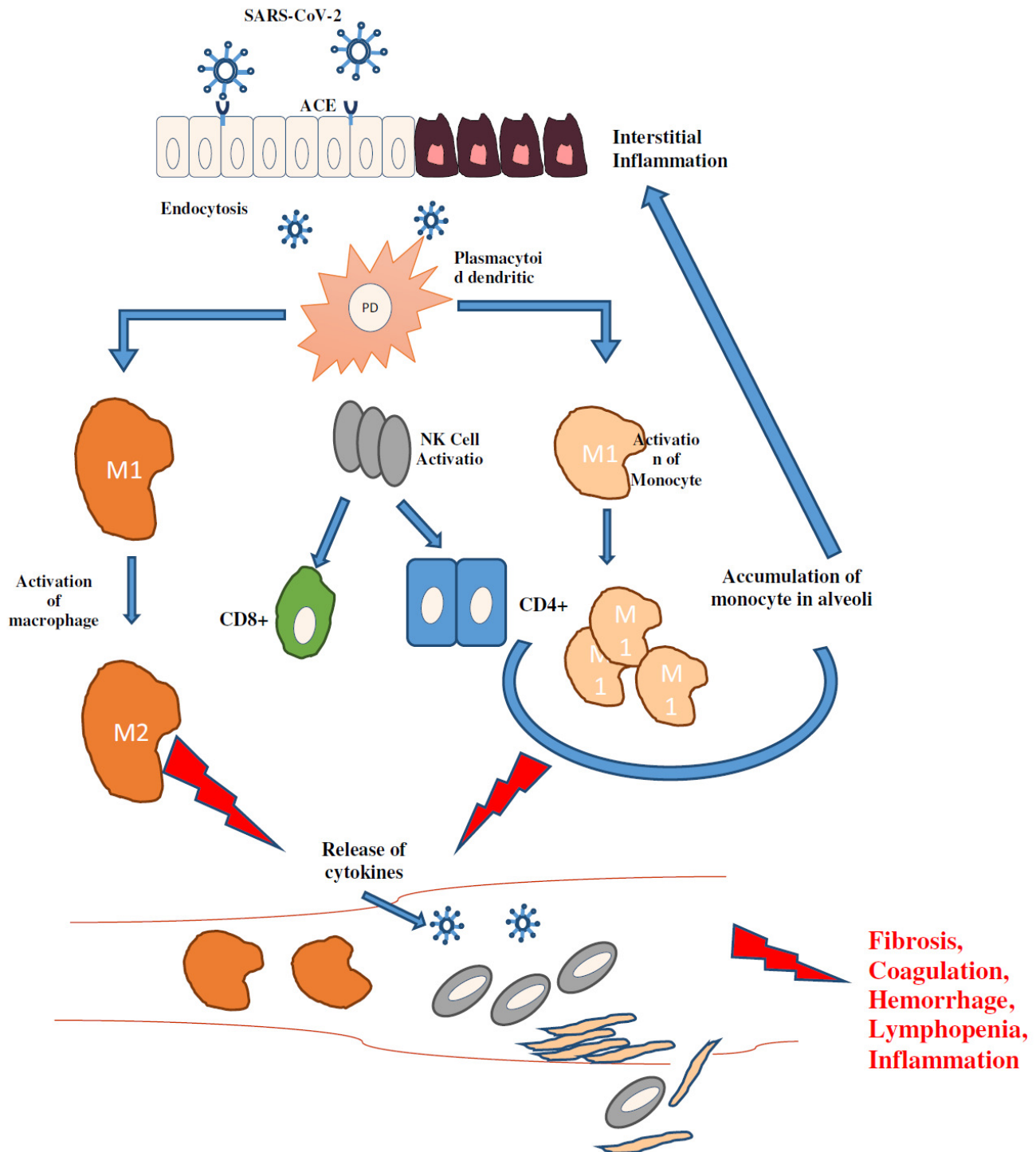
host is involved in the immune response, according to the characteristics of the SARS-CoV-2 virus (Zhou *et al.*, 2020). In five herbal medicines (*Althaea officinalis*, *Commiphora molmol*, *Glycyrrhiza glabra*, *Hedera helix*, and *Sambucus nigra*), was found to be favourable the benefit/risk assessment reported in the study. Also, 12 promising herbals reported (*Allium sativum*, *Andrographis paniculata*, *Echinacea angustifolia*, *Echinacea purpurea*, *Eucalyptus globulus essential oil*, *Justicia pectoralis*, *Magnolia officinalis*, *Mikania glomerata*, *Pelargonium sidoides*, *Pimpinella anisum*, *Salix sp.*, *Zingiber officinale*). We infer, based on the previous studies, that these herbal medicines may have the potential to monitor the synthesis and release of proinflammatory cytokines, interact with the replication of the virus in host cells, and alter some RAA-related molecular pathways. A recommendation of herbal medicine may be useful in patients. Future study of preclinical and clinical trials should be given confirmations of the herbal medicine

### Conclusion

In COVID-19, a patient's cardiovascular comorbidity is one of the identified significant contributing factors for increasing the risk of morbidity and mortality. Cardiac complications mainly include heart failure, arrhythmia, myocardial infarction, myocarditis, and coagulation abnormalities. CVS complications pose a separate risk or may be due to certain other contributing factors such as age is still unclear. In process of understanding the molecular basis and contribution of various cardiovascular complications involvement, In this comprehensive review, we aimed to highlight the role of ACE2 receptor in the implication of cardiac injury and abnormalities of the cardiovascular system, the role of cTnI in myocardial damage mechanism, the involvement of lactate dehydrogenase (LDH) and serum creatinine kinase (CK) in heart failure, myocyte necrosis, and mononuclear cell infiltrates in the pathogenesis of myocarditis, fibrin degradation products and D-dimer levels in intravascular coagulation (DIC). Furthermore, as therapies to suppress COVID-19, herbal agents may be useful.

**Table 1:** Clinical Symptoms of SARS-CoV-2 infection

	Severity Level		
	Most Common <sup>7</sup>	Less Common <sup>7</sup>	Severe Symptoms <sup>8</sup>
Clinical Symptoms of SARS-CoV-2	Fever	Headache	Difficulty breathing or shortness of breath
	Dry cough	Skin rashes	Chest pain or pressure
	Myalgia	Sputum production	Loss of speech or movement
	Pneumonia	Lymphopenia	Contractile Dysfunction
	Dyspnoea	Dyspnoea	Myocardial Necrosis
	Fatigue	Sore throat	Edema
	Sneezing	Diarrhoea	Haemoptysis



**Fig. 1:** Pathophysiology of SARS-CoV-2 infection

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