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COMMENTARY

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Papaverine, a promising therapeutic agent for the treatment of COVID-19 patients with underlying cardiovascular diseases (CVDs)

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Abstract

The causative agent of coronavirus disease-2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), enters the host cells via an angiotensin-converting enzyme 2 (ACE2)-mediated endocytosis-dependent manner. Because ACE2 is highly expressed in the heart, SARS-CoV-2 can severely infect heart tissue and arteries, causing acute and chronic damage to the cardiovascular system. Therefore, special attention should be paid to finding appropriate agents to protect this vital system during COVID-19 treatment. Papaverine is a unique vasodilator alkaloid that is clinically used in the treatment of vasospasm. Interestingly, this compound has potent and direct effects on a wide range of viruses, and could also prevent viral exploitation mechanisms of the host cell facilities by inhibiting some cellular signaling pathways such as p38 MAPK. This pathway was recently introduced as a promising target for the treatment of COVID-19. Papaverine also has anti-inflammatory effects which is useful in combating the hyper-inflammatory phase of the COVID-19. Unlike some medications that have severe dosage-restrictions in the treatment of COVID-19 due to cardiac side effects, papaverine is recommended for use in many heart disorders. The ability of papaverine to treat COVID-19 has become more promising when the results of some extensive screenings showed the strong ability of this compound to inhibit the cytopathic effects of SARS-CoV-2 with EC_{50} of 1.1 μM. Having several therapeutic effects along with desired safety profile raises this hypothesis that papaverine could be a promising compound for the suppression of SARS-CoV-2 and prevention of ischemia/vasoconstriction-related complications in COVID-19 disease, especially in patients with underlying cardiovascular diseases (CVDs).

KEYWORDS
cardiovascular diseases (CVDs), COVID-19, p38 MAPK, Papaverine, SARS-CoV-2

As is clear, coronavirus disease-2019 (COVID-19) can cause severe cardiovascular damages increasing the risk of death in patients with underlying cardiovascular disease (CVD) (Nishiga et al., 2020). Previous observations revealed that other famous beta-coronaviruses Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome coronavirus (SARS-CoV) cause remarkable cardiac complications such as acute myocarditis (Arabi et al., 2015; Oudit et al., 2009). This disorder is also significantly observed in patients with COVID-19 especially those with CVD that is detectable by increasing the level of some cardiac injury biomarkers such as

elevated highly sensitive troponin I (hs-cTnI) and creatine kinase (CK) (Guzik et al., 2020). Therefore, finding new treatments to prevent SARS-CoV-2 damage to the cardiovascular system is very important.

The angiotensin-converting enzyme 2 (ACE2) receptor plays a basic role in the infectivity of SARS-CoV-2, and also has a key role in the cardiovascular system and blood circulation (Gurwitz, 2020a). The virus enters the host cells via an ACE2-mediated endocytosis-dependent manner (Hoffmann et al., 2020). Because ACE2 is highly expressed in the lungs, acute respiratory distress syndrome (ARDS) is the most prominent feature of COVID-19 infection. ACE2 is also greatly expressed in the cardiovascular system, and has a critical role in the regulation of blood pressure through catalyzing the hydrolysis of vasoconstrictor angiotensin II (Ang II) into vasodilator angiotensin 1–7 (Ang 1–7) (Keidar et al., 2007). According to clinical observations, severe inflammatory processes and vascular contractions in cardiac patients with COVID-19 pose a high risk of death (Tomasoni et al., 2020). The mechanism of hyper-inflammation and fatal tissue damages caused by SARS-CoV-2 is not yet fully understood. Because SARS-CoV-2 depends on the use of host cell facilities for survival and replication, understanding host–cellular functions used by the virus would be essential. Given the advances in this area, scientists suggest that the Renin-Angiotensin System (RAS) and the p38 mitogen-activated protein kinase (p38 MAPK) pathway are promising targets for the treatment of COVID-19 (Dean et al., 2021; Grimes & Grimes, 2020a; Pucci et al., 2021; Sohag et al., 2020). Accordingly, the use of modulators of such cellular pathways is attracting great attention for the treatment of COVID-19 (Valipour et al., 2021).

The destructive effects of SARS-CoV-2 on endothelial and vascular function are so significant that COVID-19 has been termed a vascular disease (Siddiqi et al., 2021). As stated in previous studies, the RAS signaling pathway plays a key role in cardiovascular fluid balance and blood pressure, and its normal activity plays an important role in the treatment and survival of COVID-19 patients (Huang et al., 2020). Ang II is a potent vasoconstrictor present in this system whose activity increases peripheral vascular resistance and thus increases blood pressure. This enzyme is produced by the interaction of ACE residing in the vascular endothelium with the Ang I. By converting Ang II to Ang 1–7, Mas receptor is stimulated and provided conditions eventually lead to vasodilation, as well as suppression of inflammation, atrophy, and fibrosis (Ferrario & Strawn, 2006).

The p38 MAPK pathway is a critical cellular signaling that regulates the release of macrophage- and fibroblast-derived proteins, and proinflammatory cytokines. Some studies suggest that the inflammatory effects of Ang II are mediated by the activation of the p38 MAPK pathway, therefore, some scientists consider this pathway as a promising target for the treatment of COVID-19 (Grimes & Grimes, 2020). Also, there are many studies that highlight the role of abnormal activation of the p38 MAPK pathway in the development of heart damages. By summarizing these studies, some reviews reported that hyper-activation of this pathway leads to cardiac-related pathogenic conditions such as disruption of cardiac fibroblast function that eventually leads to serious cellular heart damages (Fisk et al., 2014; Turner & Blythe, 2019; Wang et al., 2016).

Mechanistic evaluations suggest that there is a remarkable correlation between RAS disruption and disproportionate activity of the p38 MAPK pathway in SARS-CoV-2 infectivity. When SARS-CoV-2 binds to ACE2 during cell entry and alters its normal activity, the routine conversion pathway of Ang II to Ang 1–7 is disrupted. Disruption of this pathway causes Ang II to over-affect the AT1 receptor, leading to severe inflammation and vasoconstriction following disproportionate activation of the p38 MAPK pathway (Park et al., 2007; Simões e et al., 2013). Also, other previous studies have confirmed that SARS-CoV (the closest relative of SARS-CoV-2) regulates the p38 MAPK pathway for replication and pathogenesis (Kopecky-Bromberg et al., 2006; Marchant et al., 2010).

Because p38 MAPK-inhibitors can potentially counteract the pathogenicity of SARS-CoV-2 in several ways and also do not have a direct adverse effect on the cardiovascular system, they appear to be promising therapeutic agents for the treatment of COVID-19. By that logic, some clinical trials today are evaluating the role of the p38 MAPK inhibitors in the treatment of COVID-19 patients (Clinical-Trials. gov Identifier: NCT04511819).

Papaverine is known as a vasodilator and direct-acting smooth muscle relaxant. In clinics, this alkaloid is used for the treatment of vasospasm as an effective vasodilator, especially those involving cerebral and heart disorders. This drug relaxes the smooth muscles of the coronary arteries well, and has a direct effect on the heart muscle reducing conduction and prolonging the refractory period (Wilson & White, 1986). The broad-spectrum antiviral effect is another property of this compound that has recently become more highlighted through showing potent inhibitory effect on the SARS-CoV-2 cytopathicity with $EC_{50} = 1.1\ \mu M$ (discussed below) (Ellinger et al., 2021). Previous studies have shown that papaverine can also exert its antiviral effects by modulating host cells signaling pathways such as MAPK (Aggarwal et al., 2020a; García-Cárceles et al., 2021). Furthermore, the results of a new study indicated that the potent anti-ischemic and anti-inflammatory effects of papaverine are significantly related to the regulation of the p38 MAPK pathway and modulation of neurovascular inflammation, and this compound well regulated both Th17-derived cytokine generation and the IL-17 signaling pathway by acting on p38 MAPK and IL-6 (Guan et al., 2020).

As shown schematically in Figure 1, papaverine can fight the SARS-CoV-2 pathogenicity in several ways due to its outstanding therapeutic effects which are discussed below.

In addition to having prominent vasodilatory activities, one of the most important therapeutic effects of papaverine is its broad-spectrum antiviral activity that has been reported in previous studies against a wide range of viruses. A recent study also reported that papaverine can effectively inhibit various strains of influenza and paramyxoviruses (Aggarwal et al., 2020). Importantly, papaverine has remarkable inhibitory effects against coronaviruses which was confirmed by several independent studies. A few months before the advent of SARS-CoV-2, Shen et al. performed a high-throughput screening (HTS) to find effective anti-coronavirus agents. Results of this study showed that papaverine has a broad-spectrum

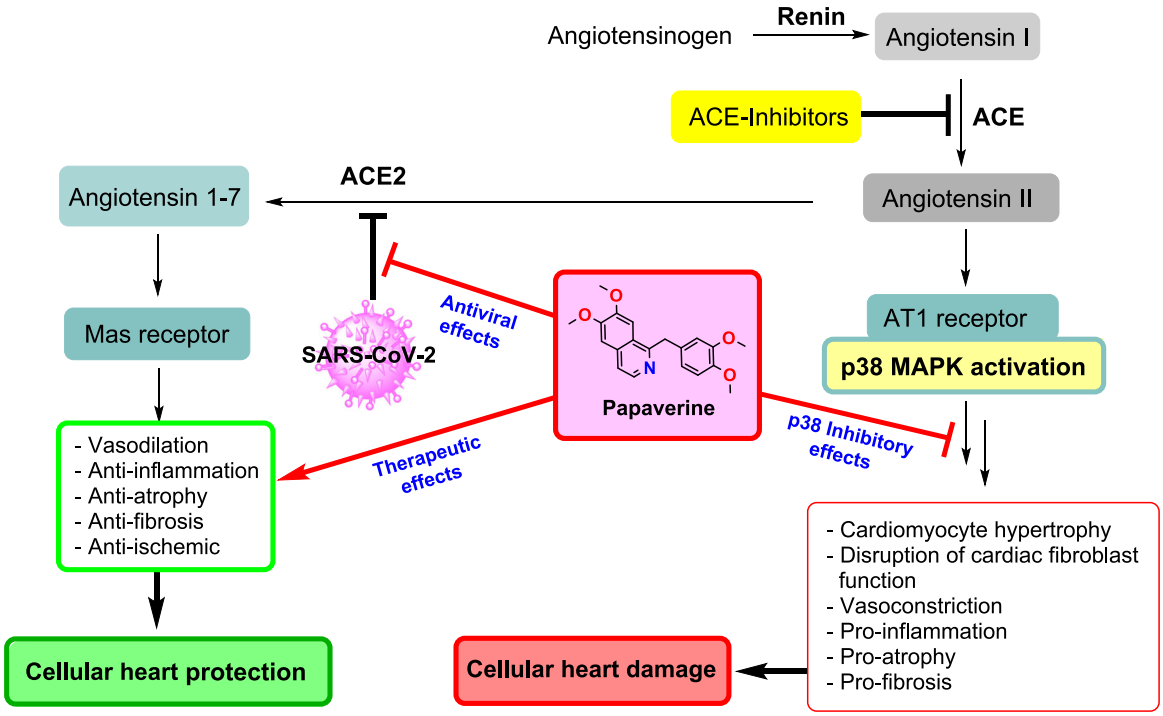

FIGURE 1 Possible pathogenesis of SARS-CoV-2, and multifunctional therapeutic effects of the papaverine against SARS-CoV-2 infection.

anti-coronavirus activity against HCoV-NL63 (EC_{50} = 7.32 μM, CC_{50} = 11.71 μM), HCoV-OC43 (EC_{50} = 1.61 μM, CC_{50} = 12.11 μM), MERS-CoV (EC_{50} = 9.45 μM, CC_{50} = 11.98 μM), and MHV-A59 (EC_{50} = 11.46 μM, CC_{50} = 12.44 μM) (Shen et al., 2019).

SARS-CoV-2 is a highly cytocidal virus that causes severe morphological changes in cardiac cells (as well as changes in cell physiology and subsequent biosynthetic events) that ultimately cause the destruction of host cells and tissues (Perez-Bermejo et al., 2021; Zhu et al., 2020). These virus-induced cellular lesions are called cytopathic effects (CPE). Bioactive compounds that can inhibit the CPE of viruses have valuable potential for clinical applications (Byrd & Hruby, 2006). This effect can occur through the effects of CPE inhibitors through both direct effects on viral targets and regulation of host-dependent factors. In a recent study, Elinger et al. performed a high-content screening on a library of 5632 compounds using the microscopy method for their ability to inhibit virus-induced structural damages in host cells resulting from SARS-CoV-2 infection in the Caco-2 cells. The results of this study also confirmed the strong ability of papaverine to reduce CPE of SARS-CoV-2 with EC_{50} = 1.1 μM, and even its analogs ethaverine and drotaverine with remarkable EC_{50} of 2.15 μM and 6.07 μM, respectively (Ellinger et al., 2021).

In summary, SARS-CoV-2 causes damage to the myocardium, and patients with cardiovascular disease are more vulnerable to COVID-19. Although cardiac side effects severely limit the use of some approved drugs with strong anti-SARS-CoV-2 activity in the treatment of COVID-19 (such as chloroquine and emetine), papaverine is probably the only anti-SARS-CoV-2 compound recommended for use in ischemia/vasoconstriction-related complications and many heart disorders such as angina pectoris, peripheral vascular disease, peripheral and pulmonary embolism, and vascular spasm associated with acute myocardial infarction. This therapeutic feature highlights the capability of papaverine to be used in the medication regimen of COVID-19 patients with underlying heart disorders. Of course, it is important to note that papaverine is contraindicated in a few heart patients, such as patients with the complete atrioventricular block (Chauhan et al., 1992).

Drug repurposing is a cost-effective strategy that can provide new treatment options to COVID-19 patients without the need for costly and time-consuming safety-related clinical trials (Gurwitz, 2020b; Phadke & Saunik, 2020). As mentioned above, papaverine could be useful in the treatment of COVID-19 patients in several ways. First, this drug has p38 MAPK inhibitory activity, so it can maintain normal heart activity by reducing vasoconstriction and inflammation caused by the disproportionate activity of this pathway. Having vasodilatory activity, is another beneficial effect of papaverine for COVID-19 patients to improve their heart function. Interestingly, papaverine has also represented strong inhibitory effects against SARS-CoV-2 cytopathicity. In addition, this compound has a good safety profile and does not cause severe side effects in the body.

Due to the beneficial effects of papaverine, this commentary suggests that this interesting drug can be considered as a new option in the medication regimen for the treatment of COVID-19 patients, especially for those with underlying CVD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

None declared.

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