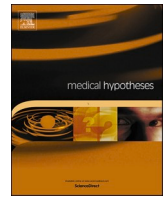




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BPC 157 as Potential Treatment for COVID-19

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ABSTRACT

The emergence of coronavirus disease (COVID-19) in China at the end of 2019 has caused a large global outbreak. COVID-19 is largely seen as a thrombotic and vascular disease targeting endothelial cells (ECs) throughout the body that can provoke the breakdown of central vascular functions. This explains the complications and multi-organ failure seen in COVID-19 patients including acute respiratory distress syndrome, cardiovascular complications, liver damage, and neurological damage. Acknowledging the comorbidities and potential organ injuries throughout the course of COVID-19 is therefore crucial in the clinical management of patients. Here we discuss BPC 157, based primarily on animal model data, as a novel agent that can improve the clinical management of COVID-19. BPC 157 is a peptide that has demonstrated anti-inflammatory, cytoprotective, and endothelial-protective effects in different organ systems in different species. BPC 157 activated endothelial nitric oxide synthase (eNOS) is associated with nitric oxide (NO) release, tissue repair and angiomodulatory properties which can lead to improved vascular integrity and immune response, reduced proinflammatory profile, and reduced critical levels of the disease. As a result, discussion of its use as a potential prophylactic and complementary treatment is critical. All examined treatments, although potentially effective against COVID-19, need either appropriate drug development or clinical trials in humans to be suitable for clinical use.

Background

At present, few treatments have been demonstrated to reduce the burden of morbidity and mortality from COVID-19. There has been little convincing evidence on interventions that may prevent disease, reduce hospitalizations, and reduce the numbers of critical disease progression and death. COVID-19 is illustrated to begin with acute respiratory distress in the lungs that moves quickly to vascular networks throughout the gut, kidney, heart, and brain with associated platelet-endothelial dysfunction and abnormally rapid blood clotting. This can lead to severe multisystemic end-organ damage such as neurological, cardiovascular and gastrointestinal complications including ischemic stroke, liver damage, intracerebral hemorrhage, encephalopathies, renal failure, pulmonary hypertension, arterial thrombosis, and myocardial infarction [41,44,99]. This is underscored in common comorbidities of COVID-19 e.g., obesity, hypertension, and diabetes, diseases characterized with disturbed EC integrity [16,65,66]. These risk factors and diseases are all related to cardiovascular complications and they account together for an overwhelming amount of global deaths and life years lost due to SARS-CoV-2 infection. A significant socioeconomic burden on societies and health care systems is the consequence of these leading risk factors. EC

dysfunction and the ensuing clotting and inflammation is a common denominator responsible, at least in part, for the multiple and varied clinical outcomes seen in COVID-19 patients [16,36,41,65,66,68]. ECs are commonly known to be active participants in the regulation of blood fluidity, platelet aggregation, vascular tone, inflammation and angiogenesis [53,55,77,93]. SARS-CoV-2 invades ECs via transmembrane angiotensin-converting enzyme 2 (ACE2) receptor, enabled by transmembrane protease, serine 2 (TMPRSS2) [44,68]. ECs as a target of SARS-CoV-2 results in damaged integrity of vessel barrier, induced oxidative stress and triggered inflammatory dynamics across different organ systems which promotes pro-coagulative state and excessive infiltration of cytokines and chemokines into multiple organs [41]. ECs provide a conduit for antigen transport for infected cells and immune-cell trafficking from infected organs to secondary lymphoid organs [9,51]. In deceased patients, SARS-CoV-2 was found in ECs in vessels of multiple tissues including lungs, brain stem, heart, liver, kidneys, and pancreas [9]. ECs as a target for SARS-CoV-2 contributes to infection manifestations including acute respiratory distress syndrome, strokes, cardiac injury, liver injury, frequent causes of mortality in COVID-19 patients [26,65,66,68].

Here we focused on the stable gastric pentadecapeptide, BPC 157 as a

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potential treatment for COVID-19 patients. BPC 157 is a peptide that has demonstrated anti-inflammatory, cytoprotective, and endothelium-protecting effects in different organ systems in various species. BPC 157 has been reviewed as a likely mediator of Robert's stomach cytoprotection/adaptive cytoprotection and organoprotection model [73–74,79,80], (2018). BPC 157 is largely known as an antiulcer agent, shown to be effective in inflammatory bowel disease and multiple sclerosis clinical trials in humans with no side effects (PL 10, PLD 116, PLD 14736, Pliva, Croatia) [34,39,82,85,84,83]. Preclinical safety evaluation of BPC 157 has concluded it can act as a potential drug for treating various wounds [106]. In animal models, BPC 157 is a proven therapy to treat damage in various organ systems such as the gastrointestinal tract, cardiovascular system, central nervous system (CNS). BPC 157 application reduced oxidative stress [7,20,23,59,103,104], alleviated thrombosis [34,49,91] ameliorated endothelial injury [35,73,78,87,80] recovered disturbances in vasculature [7,73,103], has beneficial effects on inflammation, edema, wound healing in several organs [27,38,39,92,95], regulated platelet function after challenge with aspirin, clopidogrel and cilostazol [21,50], and modulated nitric oxide (NO) systems [27,35,70,69,78,86,96]. Here we present the research regarding BPC 157 as a protective agent that exerts pleiotropic effects on organs targeted from COVID-19, particularly the heart, the liver, and the brain.

Hypothesis

Here we hypothesize BPC 157 to be a promising treatment for COVID-19 patients. Plausibly, BPC 157 may offer improved COVID-19 outcomes by mitigating cytokine derailment and subsequent multi-organ failure based on its anti-inflammatory, cytoprotective, and endothelium-protecting effects (e.g., through BPC 157-eNOS interactions). Furthermore, BPC 157 applications may obstruct viral replication, improve clinical and biochemical parameters, attenuate organ damage from the systemic alterations, provoked from SARS-CoV-2.

Support for Hypothesis

BPC 157 as an eNOS Promoter

BPC 157 is predominately shown to interact eNOS, NO system, and counteracted the adverse effect of L-NAME (i.e., hypertension; lack of NO release in vitro) and L-arginine (i.e., hypotension; NO over-release in vitro) [35,46,73–74,78]. BPC 157 applications have directly shown to modulate the vasomotor tone of an isolated aorta in a concentration- and NO-dependent manner via the activation of Src-Cav-1-eNOS pathway in rats. At higher concentrations, BPC 157 slightly increased vasorelaxation in the aorta independent from endothelial activation [35]. Severe cases of COVID-19 patients can lead to the loss of eNOS activity or eNOS uncoupling by adverse regulation of redox switches in eNOS and its up-/down-stream signaling molecules. Endothelial integrity and cellular defense requires eNOS function and its ability to generate NO [17,67]. Among the pleiotropic cardiovascular actions of eNOS, the stimulation of NO production underlies major mechanisms that exert anti-apoptotic, anti-inflammatory and oxidative/nitrative-suppressive effects. Ultimately, a pivotal vector that supports endothelial integrity and permeability. NO release is the most studied mediator in the modulation of vascular tone via relaxation of smooth muscle cells, has an antithrombotic role due to the attenuation of platelet activation and aggregation, regulates the migration and adhesion of leukocytes on EC, and inhibits vascular smooth muscle cell proliferation. NO deficiency is indicative of injured vessels; ultimately related to hypertension and thrombus formation frequently seen in severe COVID-19 patients. In practice, NO has shown to be clinically effective in the treatment of congenital heart disease, mitral valvular disease combined with pulmonary hypertension and in orthotopic cardiac transplantation patients.

Notably, eNOS function and activity in the endothelium is not the sole mechanism essential for vascular integrity and homeostasis. Nonetheless, this signaling pathway represents an attractive target for pharmacological therapy of COVID-19 and various cardiovascular diseases.

In addition to NO's pivotal role in vasculature maintenance, NO has some anti-viral properties in the body. NO reportedly interferes with the interaction between coronavirus viral S-protein and its cognate host receptor, ACE-2 [4]. NO or its derivatives has shown to cause a reduction in viral RNA production in the early steps of viral replication, including coronaviruses based on various in vitro and in vivo studies [3,5,4,61,2]. Non-specific antiviral effects of NO have been reported in a variety of viral infections, including HIV, vaccinia virus, enterovirus and coronavirus [31,63,29,107,2]. NO has several direct modes of action as an antiviral agent. NO is involved in viral enzyme inhibition through nitrosylation of viral proteins [14,32,33,72]. Specifically, NO-mediated S-nitrosylation of viral cysteine proteases and host serine protease, TMPRSS2 are both critical in viral cellular entry, and seem to be NO sensitive [32,33,40,47,65] modulation of viral-encoded transcription factors. NO inactivates the protease 3C, an enzyme essential for coronavirus replication and is considered an important therapeutic target for diseases caused by coronaviruses, including COVID-19. NO S-nitrosylated the cysteine residue in the active site of protease 3C, inhibiting protease activity and interrupting the viral life cycle [63,31,29]. NO-based therapies (e.g., inhaled NO) have demonstrated success in clinical settings for the treatment of past respiratory viruses. and was shown to relieve the cardiopulmonary and vascular complications from SARS-CoV-2 infection [6,24]. Inhaled NO is suggested as a useful intervention for COVID-19 in multiple stages such as prevention or therapy, including prevention of infection, intervention of mild patients, alternative rescue treatment of moderate and severe patients, and adjuvant treatment of mechanically ventilated patients. While eNOS-derived NO has been shown to inhibit microbial growth from mycobacterium tuberculosis in the lymphatic system when the ECs represent the site of microbial invasion [54], eNOS derived NO implications on COVID-19 patients has not been investigated. Theoretically, it is plausible BPC 157-eNOS/NO interactions may be an early treatment by lowering viral burden and attenuating platelet-endothelial dysfunction and associated thrombosis.

BPC 157 Cardioprotective Applications in Animal Studies

BPC 157 endothelial protective and cytoprotective effects have led to its investigation as an angio-modulatory agent in animal models. BPC 157 administration has consistently supported blood vessel recruitment in response to blood vessel disturbances (i.e. perforation, obstruction, occlusion) [7,73,103]. BPC 157 has shown to prevent and resolve inferior cava vein hypertension [25,103], pulmonary hypertension [27,86,97], disturbances in hepatic arteries [39,49,79], portal vein tributaries [25,49], deep vein thrombosis in rodents subjected to arterial clamping [49,104], reduced the duration of arrhythmias during hypoxia and reoxygenation in isolated guinea pig hearts [8], treated congestive heart failure in mice and rats subjected to doxorubicin, bupivacaine, and lidocaine induced cardiotoxicity [57,58,90,108]. Cardiac injury alleviation from BPC 157 was measured in remediated heart beats i.e., ventricular tachycardia, bradycardia, T-wave elevation, QTc prolongation and asystole in rats [57,58,90,108]. Further, BPC 157 in a single application, counteracted right heart failure induced by acute thrombotic coronary occlusion in rats by reigning in increased P wave amplitude, tachycardia and ST-elevation [57,58,90,108]. BPC 157 also prevented pulmonary interstitial edema and reduced lymphocyte count and capillary congestion [25]. In the same vein, BPC 157 has shown to counteract lung lesions in rodent models [89]. This is notable, as these outcomes mimic the outcomes seen with acute respiratory distress syndrome evoked from SARS-CoV-2 [1,100]. In rats subjected to monocrotaline-induced pulmonary arterial hypertension BPC 157 applications prevented pulmonary hypertension and advanced pulmonary hypertension was rapidly attenuated and then completely eliminated

[97]. Moreover, Vukojevic et al. demonstrated BPC 157 application as a therapy Virchow's triad in rats (e.g., the prevention and reversal of both caval hypertension and aortic hypotension; counteracted the effects and residual effects of tachycardia, thrombosis, and thrombocytopenia) [103]. These effects were, at least in part, carried out through increased Egr, Nos3, Srf, and Kras and decreased Egr1, Vegfr2, and Pley [103]. Increased Nos3 and decreased Vegfr2, despite the strictly Vegfr2 promoting effects of many growth factors and peptides, are discussed as therapeutic strategies for SARS-CoV-2 damage in the cardiovascular system [44]. Virchow's triad has established overlap with the common complications in severe COVID-19 outcomes in patients such as endothelial injury, hypercoagulability, and thromboembolic risk in COVID-19 patients [62]. The compiled findings suggest BPC 157, in animal models, is an effective therapy for disturbances in the cardiovascular system that are commonly seen in COVID-19 patients. These disturbances include venous thromboembolism and coagulopathy from inflammatory and vascular disturbances, myocardial damage, arrhythmias, and pulmonary embolisms and may enhance the therapy for acute respiratory distress syndrome.

BPC 157 Lung and Liver Applications

Liver damage is associated with outcomes in COVID-19 patients [37,60,105]. Data from observational studies illustrates the association between comorbid chronic liver disease, acute liver injury and inflammation. In COVID-19 patients, cytokine production and elevated elevations in liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactic dehydrogenase (LDH), creatine kinase (CK), gamma-glutamyl transferase (GGT), and bilirubin levels and outcomes of COVID-19 hospitalized patients [15,37,60,105]. BPC 157 applications have persistently demonstrated favorable outcomes in the liver by resolving gastrointestinal lesions, bile duct ligation, liver lesions and hepatic encephalopathy in rodent models [25,38,39,56,70,69,76,87]. Interestingly, there is an observed relationship between liver damage and chronic lung disease [13,52,75]. Kolovrat et al. reinforced this notion, by using BPC 157 therapy in rats subjected to Pringle maneuver i.e., portal triad obstruction where BPC 157 rapidly activated portacaval shunt, normalized arterial and disturbed blood pressure, counteracted formation of blood clots and cardiac rhythm changes and counteracted gastrointestinal mucosal lesion and lung lesions [49]. Further, in rats mice subjected to congestive heart failure, 4 week administration of BPC 157 counteracted raised serum liver enzyme values ALT, AST, ALP, LDH, CK in ug dosage of BPC 157 in rats [57]. Likewise, in research investigating BPC 157 on liver lesions, BPC 157 counteracted increased liver enzymes AST, ALT, ALP, [20,76], and GGT and total bilirubin [39,76,79] as well as decreased IL-6, TNF- α , IL-1 β levels in liver tissue [76]. In summary, BPC 157 has shown to reign in inflammatory cytokines and promote function in both the lung and liver in animal models, and may recover damage from inflammation and cytokine release in these organs provoked from COVID-19 [12,22,30,45].

BPC 157 Neuroprotective Applications in Animal Models

COVID-19 can cause profound molecular changes induced by inflammation in the brain. More specifically, induced significant cytokine and chemokine production, infiltration of peripheral immune cells, edema, increased blood-brain barrier (BBB) permeability and breakdown [64]. This leads to neurological complications frequently seen in COVID-19 patients include encephalopathies, strokes, peripheral nerve damage [19,32,64]. BPC 157 has demonstrated beneficial effects on CNS, an organ system with established vulnerability to SARS-CoV-2 onset [11,43,64,94,95]. BPC 157 can act through different vasoactive pathways and systems that promote hippocampal neuron survival and growth that has demonstrated bidirectional effects on the gut-brain axis. In rodent models BPC 157 reduced both immediate and delayed damage

induced by brain trauma [95,104] counteracted brain lesions from cuprizone [48,85] counteracted brain encephalopathies from alcohol usage (acute and chronic) [70,69,87], NSAIDs, and insulin overdose [38,85]. In operated rats subjected to bilateral carotid artery occlusion, BPC 157 remedied both early and delayed neural hippocampal damage, resolved ischemia/reperfusion injuries in rats and consequently theorized as a therapeutic intervention for stroke [104]. This therapeutic effect of BPC 157 was observed to be carried out by elevated Egr1, Akt1, Kras, Src, Foxo, Srf, Vegfr2, Nos3, and Nos1, and decreased Nos2, NF- κ B [104]. Increased expression of Nos3, Nos1, and decreased expression of Nos2, NF- κ B have all been theorized as strategic therapeutic targets in mitigating COVID-19 effects on the brain [64]. NO released by Nos3 and Nos1 scavenges oxygen free radicals, inhibits the expression of adhesion molecules, and regulates platelet aggregation and lymphocyte adhesion in the brain [42,98]. Furthermore, BPC 157 applications decreased NF- κ B, Nos2 gene expression and decreased pro-inflammatory gene Cox-2 in intestinal, liver and brain lesions in rats [20,56]. These decreases are implicated with reduced binding of TNF- α release. Modulating NF- κ B, Nos2 and inhibiting TNF- α , Cox-2 release have been targets that can derail the inflammatory cytokine buildup seen in COVID-19 patients [30,102]. These functions are important for cerebral microvascular tone regulation, BBB integrity, and procoagulant stimulation [18,88]. Further, BPC 157 has shown to modulate neurotransmitter systems such as dopaminergic [82], serotonergic [94], GABAergic [43], and opioid systems [10]. Reestablishing homeostasis in these neurotransmitter systems allows better resilience for COVID-19 patients. Together these findings suggest BPC 157 applications may relieve the neuro-inflammatory and cerebrovascular complications from COVID-19 such as encephalopathies, strokes, peripheral nerve damage, inflammation of the brain. These mechanisms are considered therapeutic targets in the management and treatment of patients with COVID-19.

Limitations

BPC 157 is a clinical infant with a limited number of published clinical trials in humans, and is investigated among a limited number of labs. Many of the cited studies have not considered potential negatives associated with the use of BPC 157, as well as no clear conflicts in literature-based ideas being seen. The reviewed research is limited in terms of microscopic level measures in various investigations. As a result, the scope of BPC 157 efficacy is incomplete. At present, the majority of studies are predominantly limited to mostly animal models and the efficacy of BPC 157 in humans has not been explored extensively. Since there are obvious differences between rodent and human physiology, caution needs to be practiced in extrapolating the efficacy of novel agents to clinical applications in humans. However, it should be underscored BPC 157 is a peptide derived from human gastric juices, and its stability and protective effect of BPC 157 has been widely reported. The emphasis about the relative paucity of the BPC 157 in human clinical data should not be not be discounted [28,74,83,81]. BPC 157 was proved to be efficacious and safe in the available clinical trials in humans for inflammatory bowel disease, mild to moderate ulcerative colitis (PL-10, PLD-116, PL14736, Pliva, Croatia) [101,71]. A multicenter, randomized, double blind, placebo-controlled phase II study of PL 14,736 enema in the treatment of mild-to-moderate ulcerative colitis as well as in the experimental rats' studies [23]. It has been established to have a very safe profile (LD1 could be not achieved, no side effects in clinical trials) [71,74], 2020). This point has been recently reinforced, in preclinical safety evaluation of BPC 157 in both chronic and acute applications [106]. Therefore, some level of safety in human subjects can be assumed.

Conclusion

BPC 157 proposes many potential effects to treat a range of conditions. Notably, BPC 157-eNOS interactions represents an attractive

therapeutic target that has not yet been pharmacologically employed in COVID-19 patients. Furthermore, BPC 157 plays a role in several biological gene expressions and has demonstrated pleiotropic immunomodulatory properties that have proven extensive beneficial effects in animal models, resolving both localized and systemic damage of soft tissues. BPC 157 has persistently exhibited anti-arrhythmic, endothelial-protective and anti-inflammatory effects and has shown to prevent and reverse thrombosis formation, maintain platelet function, alleviate peripheral vascular occlusion disturbances in animal models. All attributing factors to COVID-19 outcomes. As a result, BPC 157 poses as a necessary candidate in need of extensive investigation in preventing severe COVID-19. In animal models, BPC 157 has improved liver enzyme profile and disturbances, lung disturbances, cardiovascular disturbances, cerebrovascular disturbances and promoted homeostasis among neurotransmitter systems. All common complications in COVID-19 patients that can lead to morbidity or long-haul COVID-19. Although in vivo studies of animal models revealed a broad range of protective effects of BPC 157, clinical trials in humans are relatively limited and are necessary to appraise the potential efficacy and scope of BPC 157 in clinical settings for COVID-19. Currently there is insufficient data to conclude either for or against the use of BPC 157 for the treatment of COVID-19 in humans. Nevertheless, all the studies to date that have tested BPC 157 have demonstrated substantial positive healing effects for various injury types in various organ systems. Theoretically, in early stages of the infection, BPC 157 may obstruct viral replication, improve blood vessel integrity, and suppress the onset of virus-induced cytokine cascades. In late stages of the disease, it may facilitate recovery of damaged tissues from severe COVID-19. In addition, BPC 157 as a therapeutic intervention may be a tool to further delineate the relationship between cerebrovascular, cardiovascular, liver and lung toxicity seen in COVID-19 infections. Future clinical trials are needed to prove the potential therapeutic use of BPC 157 in COVID-19 patients.

Ethics

No animal experimentation was used in this paper. The animal-related studies compiled for the purposes of this paper were carried out to high ethical standards.

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Declaration of Competing Interest

The authors declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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