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The combination of bromelain and curcumin as an immune-boosting nutraceutical in the prevention of severe COVID-19

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic is still ongoing, while no treatment has been proven effective. COVID-19 pathophysiology involves the activation of three main pathways: the inflammatory, the coagulation and the bradykinin cascades. Here, we highlight for the first time the joint potential therapeutic role of bromelain and curcumin, two well-known nutraceuticals, in the prevention of severe COVID-19. Bromelain (a cysteine protease isolated from the pineapple stem) and curcumin (a natural phenol found in turmeric) exert important immunomodulatory actions interfering in the crucial steps of COVID-19 pathophysiology. Their anti-inflammatory properties include inhibition of transcription factors and subsequent downregulation of proinflammatory mediators. They also present fibrinolytic and anticoagulant properties. Additionally, bromelain inhibits cyclooxygenase and modulates prostaglandins and thromboxane, affecting both inflammation and coagulation, and also hydrolyzes bradykinin. Interestingly, curcumin has been shown in *silico* studies to prevent entry of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells as well as viral replication, while a recent experimental study has demonstrated that bromelain may also inhibit viral entry into cells. Notably, bromelain substantially increases the absorption of curcumin after oral administration. To the best of our knowledge, this is the first report highlighting the significance of bromelain and, most importantly, the potential preventive value of the synergistic effects of bromelain and curcumin against severe COVID-19.

The worldwide spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been devastating so far, affecting more than 45 million people and causing more than 1 million deaths globally, as of November 2, 2020 [1]. Research efforts in the quest for an effective treatment for the coronavirus disease 2019 (COVID-19) have been fruitless, while our hopes to contain the pandemic lie with the development of vaccines. Recent research has revealed that the binding of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2) receptor initiates three main pathways: 1) the inflammatory, 2) the coagulation and 3) the bradykinin cascades [2,3]. The activation of these pathways varies widely between individuals leading to a wide range of clinical manifestations of COVID-19 from asymptomatic to severe acute respiratory distress syndrome, multiple organ failure and death [2].

Interestingly, a number of natural agents have received attention due to potential anti-inflammatory and anti-oxidant properties. Among these products, collectively named nutraceuticals, curcumin and bromelain comprise two bioactive substances with potent anti-inflammatory and anticoagulant actions [4,5]. Here, we present the mechanisms of action of curcumin and bromelain interfering in the crucial steps of the pathophysiology of COVID-19, and propose a potential therapeutic role in the prevention of severe

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; COX-2, cyclooxygenase-2; NF-κB, nuclear factor kappa B; PG, prostaglandin; SARS-CoV, severe acute respiratory syndrome coronavirus; STAT-3, signal transducer and activator of transcription 3; TMPRSS-2, *trans*-membrane serine protease 2; TXA2, thromboxane A2.

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COVID-19.

Curcumin (diferuloylmethane) is a natural phenol found in turmeric (*Curcuma longa)*, a member of the ginger family of plants [4]. Curcumin modulates inflammation preventing the subsequent cytokine storm by inhibiting multiple transcription factors such as nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT-3), and downregulating the proinflammatory cytokines, as this has been demonstrated in human macrophages after influenza virus infection [4,6]. Additionally, curcumin inhibits ACE modulating angiotensin II synthesis and downregulating inflammation, while it also promotes fibrinolysis and the anticoagulation process [4,6,7] (Fig. 1).

The antiviral actions of curcumin against multiple viruses (influenza and hepatitis viruses, herpes viruses, human papilloma virus, human immunodeficiency virus, severe acute respiratory syndrome coronavirus and other coronaviruses), bacteria and fungi have been established by experimental evidence [8]. Remarkably, recent evidence from *in silico* studies has demonstrated that curcumin prevents SARS-CoV-2 entry into cells by blocking the viral binding sites and the cell ligands (spike protein, ACE-2 receptors and basigin), downregulating *trans*-membrane serine protease 2 (TMPRSS-2), and by interfering with viral replication through the interaction with various viral proteins [4]. However, the minimal absorption of curcumin following oral administration presents a major limitation in its bioavailability [6].

Bromelain is a cysteine protease, isolated from the pineapple stem (*Ananas comosus*) [9]. Traditionally, it has been used for its anti-inflammatory and healing effects in cases of arthritis and injury, while it has been approved in Europe for the debridement of burn wounds. Experimental studies have demonstrated that bromelain presents unique immunomodulatory actions: 1) downregulation of the pro-inflammatory prostaglandin E−2 (PGE-2) through inhibition of NF-kB and cyclooxygenase 2 (COX-2); 2) upregulation of the anti-inflammatory PGE-1; 3) activation of inflammatory mediators (interleukin 1β, interleukin-6, tumor necrosis factor-α and interferon-γ) as an acute response to cellular stress, but also inhibition of inflammatory mediators in states of overt cytokine production; 4) modulation of T cell responses *in vitro* and *in vivo*; and 5) enhancement of T-cell dependent antigen-specific B cell antibody responses [5,10−14].

Importantly, bromelain exerts dose-dependent anticoagulant effects: 1) downregulation of PGE-2 and thromboxane A2 (TXA2), thus leading to relative excess of prostacyclin; 2) promotion of fibrinolysis by stimulating the conversion of plasminogen to plasmin and prevention of platelet aggregation. Bromelain also hydrolyzes bradykinin and reduces kininogen and bradykinin levels in serum and tissues, improving inflammation and edema as shown in animal studies [15]. Notably, the latter action supports a potential role of bromelain in alleviating COVID-19 symptoms such as cough, fever and pain, and the more serious implications of inflammation, thrombosis and edema (Fig. 1). The effect of bromelain on PGE-2 inhibition exceeds that of prednisone and aspirin, presenting very low toxicity and no major side effects [12,16].

Clinical studies have demonstrated multiple beneficial effects of bromelain in trauma, ischemic injury, hypertension, atherosclerosis, inflammatory bowel disease, arthritis, and sinusitis as well as antibacterial and antifungal properties [5]. Interestingly, a recent experimental study demonstrated that bromelain inhibits infection of VeroE6 cells by SARS-CoV-2 through blocking the virus binding

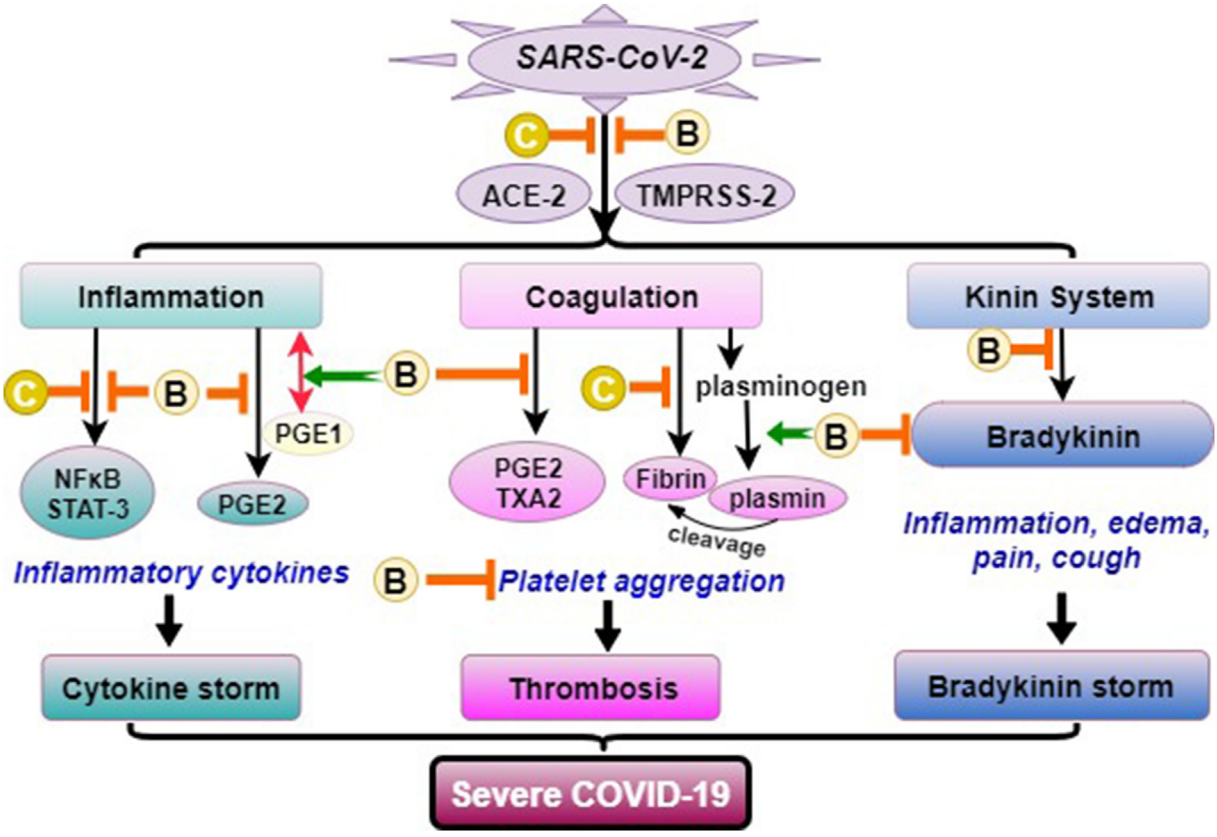

Fig. 1. Bromelain (B) and curcumin (C) exert multiple immunomodulatory actions interfering in the crucial steps of COVID-19 pathophysiology. ACE-2, angiotensin-converting enzyme 2 receptor; COVID-19, coronavirus disease 2019; NF-κB, nuclear factor kappa B; PG; prostaglandin; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2; STAT-3, signal transducer and activator of transcription 3; TMPRSS-2, *trans*-membrane serine protease 2; TXA2, thromboxane A2.

and entry into cells via downregulation of ACE-2 and TMPRSS2 expression, and cleavage of the SARS-CoV-2 spike protein, presenting a novel promising therapeutic option that warrants further investigation [17].

Due to its proteolytic action, bromelain is absorbed directly when administered orally, while it substantially promotes the absorption of curcumin enhancing its bioavailability, and making this a perfect combination of immune-boosting nutraceuticals with synergistic anti-inflammatory and anticoagulant actions [12,16].

To the best of our knowledge, this is the first report highlighting the significance of bromelain and, most importantly, the potential value of the synergistic effects of bromelain and curcumin against COVID-19. The hypothesis that this combination of nutraceuticals may prove useful for the protection against SARS-Co-V-2 infection warrants clinical investigation. Noteworthy, the favorable safety profile of this nutraceutical combination makes a compelling case for its use in the general population with potentially important implications in preventing severe COVID-19.

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Declaration of competing interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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