AARDS
COVID-19 LONG HAULER CLINIC

Preventing and Treating Long-Haul COVID-19 and Other Types of Inflammation

All active ingredients being included are considered GRAS in the US. **Generally recognized as safe (GRAS)** is a United States Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts.

Bromelain

Bromelain inhibits SARS-CoV-2 infection via targeting ACE-2, TMPRSS2, and spike protein:

Recently, studies have shown that SARS-CoV-2 homotrimeric viral spike protein (S1) binds to the Transmembrane Serine Protease 2 (TMPRSS2) primed host cell's receptor ACE-2 for initial entry, followed by S2-mediated membrane fusion.[8] Of several normal and cancerous cells tested, VeroE6 and Calu-3 cells showed ACE-2 protein expression (Fig. **1A**), as well as a basal level of TMPRSS2 protein (Fig. **1B**). Since ACE-2[9] and TMPRSS2 (UniProtKB-O15393) contains cysteine residues with disulfide bonds to stabilize the protein structure, we investigated the effect of bromelain on ACE-2 and TMPRSS2 expression. Bromelain-induced a dose- and time-dependent reduction of ACE-2 and TMPRSS2 expression in VeroE6 cells (Fig. **1C and D**) but do not alter ACE-2 expression in Calu-3 cells (Fig. **1E**). However, bromelain reduces the expression of TMPRSS2 in Calu-3 (Fig. **1E**) and ACE-2 negative normal bronchial epithelial (BEAS-2B) and lung adenocarcinoma (A549) cells (Fig. **1F and G**).

Since bromelain digested ACE-2 and S-ectodomain, we investigated the effect of bromelain on the interactions of S-ectodomain and SARS-CoV-2 with VeroE6 cells. Bromelain significantly reduced the binding of S-protein to VeroE6 cells (Fig. **3A and B**) and was further confirmed by cysteine protease inhibitor (E-64) treatment (Fig. **3C**). Interestingly, bromelain pre-treatment significantly decreased SARS CoV-2 viral binding in VeroE6 cells (P = .0021) (Fig. **3D**). Most importantly, VeroE6 cells or SARS-CoV-2 or both with bromelain reduces the viral infection (Fig. **3E and F**). Additionally, we found significantly reduced SARS-CoV-2 viral RNA copies in bromelain-treated VeroE6 (P = .0010) and Calu-3 (P = .0099) cells (Fig. **3G and H**, respectively). Collectively, these results suggest that bromelain could inhibit SARS CoV-2 binding and infection in VeroE6 and Calu-3 cells.

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Bromelain: A Review on its Potential as a Therapy for the Management of Covid 19:

Coronavirus Disease 2019 is a wide-spreading severe viral disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) virus that needs to be urgently eradicated. SARS COV-2 has infected millions of people worldwide and results in more than three hundred thousand deaths. Several repurposed drugs have failed to successfully eradicate the infection. Multiorgan failure caused by pronounced inflammation and systemic coagulation accounts for severe complications and death associated with diseases. Bromelain appears to be a potential candidate that may be used to inhibit or prevent the symptoms of the diseases. Its anti-inflammatory and anticoagulatory properties make it a potential agent that may slow the progression of the disease. In this review, we highlighted the beneficial effects of bromelain based on both experimental and clinical evidence that make bromelain a good candidate for the treatment of symptoms of CoVID-19 infection.

https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/en/covidwho882015

Properties and Therapeutic Application of Bromelain:

Osteoarthritis is the most common form of arthritis in Western countries; in the USA the prevalence of osteoarthritis ranges from 3.2 to 33% dependent on the joint [29]. A combination of bromelain, trypsin, and rutin was compared to diclofenac in 103 patients with osteoarthritis of the knee. After six weeks, both treatments resulted in significant and similar reduction in the pain and inflammation [30]. Bromelain is a food supplement that may provide an alternative treatment to nonsteroidal anti-inflammatory drugs (NSAIDs) [31]. It plays an important role in the pathogenesis of arthritis [32]. Bromelain has analgesic properties which are thought to be the result of its direct influence on pain mediators such as bradykinin [33, 34]. The earliest reported studies investigating bromelain were a series of case reports on 28 patients, with moderate or severe rheumatoid or osteoarthritis [35].

Bromelain influences blood coagulation by increasing the serum fibrinolytic ability and by inhibiting the synthesis of fibrin, a protein involved in blood clotting [47]. In rats, the reduction of serum fibrinogen level by bromelain is dose dependent. At a higher concentration of bromelain, both prothrombin time (PT) and activated partial thromboplastin time (APTT) are markedly prolonged [48]. *In vitro* and *in vivo* studies have suggested that bromelain is an effective fibrinolytic agent as it stimulates the conversion of plasminogen to plasmin, resulting in increased fibrinolysis by degrading fibrin [49, 50].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529416/

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Potential role of bromelain in clinical and therapeutic applications:

Bromelain is widely administered for its well-recognized properties, such as its anti-inflammatory, antithrombotic and fibrinolytic effects, anticancer activity and immunomodulatory effects, in addition to being a wound healing and circulatory improvement agent.

Inflammation is pivotal in the development of cancer during cellular transformation, proliferation, angiogenesis, invasion and metastasis. It has been demonstrated that suppression of chronic inflammation may reduce the cancer incidence and also inhibit cancer progression (16). Cyclooxygenase 2 (COX-2) is an important component of cancer-associated inflammation that is involved in the synthesis of prostaglandin E2 (PGE-2). PGE-2 is a proinflammatory lipid that also acts as an immunosuppressant, as well as a promoter of tumor progression (17). COX-2 converts arachidonic acid into PGE-2 and promotes tumor angiogenesis and cancer progression (18). It has been shown that bromelain downregulates COX-2 and PGE-2 expression levels in murine microglial cells and human monocytic leukemia cell lines (19). Bromelain activates the inflammatory mediators, including interleukin (IL)-1β, IL 6, interferon (INF)-γ and tumor necrosis factor (TNF)-α in mouse macrophage and human peripheral blood mononuclear cells (PBMC) (20–22). These results indicated that bromelain potentially activates the healthy immune system in association with the rapid response to cellular stress. Conversely, bromelain reduces IL-1β, IL-6 and TNF-α secretion when immune cells are already stimulated in the condition of inflammation-induced over production of cytokines (23,24). Studies have shown that bromelain reduced the expression of INF-γ and TNF-α in inflammatory bowel disease (25).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4998156/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808895/

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