



Mini Review

Bromelain: A potential therapeutic application in SARS-CoV-2 infected patients

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Abstract

The SARS-CoV-2 infection has led to a global pandemic which has led to almost 4 million deaths worldwide. However, to date, a specific antiviral drug does not exist to treat the disease and control the virus. Here, we focus on the potential use of bromelain in line with its anti-oxidant, anti-inflammatory, and immunomodulatory effects. Additionally, bromelain exerts fibrinolytic, anti-invasive and antithrombotic activities that may become a therapeutic candidate against SARS-CoV-2 infection. In this paper, we focused on bromelain's therapeutic potential concerning its potential role in reducing the severity of symptoms and the adverse effects of other antiviral drugs currently being used. The therapeutic effects of bromelain suggests that it may reduce mortality and morbidity rates in patients with CoVID-19 infections, through its anti-oxidant, anti-inflammatory, immunomodulator and anticoagulant effects. These positive effects leads us to propose that bromelain may be clinically valuable in the treatment of COVID-19 and that its therapeutic attributes should be fully investigated.

Background

Known as SARS-CoV-2, COVID-19 continues its negative impact on the world with its increasing morbidity and mortality rate [1]. Although the attempted control of the pandemic has been focused on the development of novel vaccine studies, the fact that the virus has reached a dangerous level through multiple mutations, there is necessity to develop new radical treatments and prophylactic measures. The most critical factor limiting treatments is the negative potential for side effects due to the high doses of drugs delivered in the treatments so far [2]. For this purpose, the importance of immunomodulatory agents with high therapeutic index, which have anti-oxidant and anti-inflammatory properties, which can reduce the side effects of these drugs and play a role in the modulation of the immune system and prevent the devastating effects of a cytokine storm [3]. As a potential alternative treatment for COVID-19 we propose that bromelain, a phytotherapeutic drug, may provide an alternative solution.

Bromelain

Bromelain is a group of enzymes present in all parts of the pineapple plant (*Ananas comosus*), whose enzyme's first isolation was accomplished in 1891 [4,5]. Despite being found in all parts of the pineapple, extracts from the seed are commercially preferential. Bromelain extract is a mixture of different enzymes (thiol endopeptidases and phosphatase, glucosidase, peroxidase, cellulase), glycosidase-like components, carbohydrates, glycoproteins and several protease inhibitors.

Extensive data has been collected from numerous studies on the administration of large doses of bromelain, which are based on close or similar models, which have yielded varying results. Bromelain's LD50 is >10 g/kg in rodents, 12 g/day orally is a safe dose for humans, without significant side effects [6,7].

Bromelain contains cysteine proteinases that have differences in proteolytic activity. It is unclear how bromelain

proteinases contribute to anti-inflammatory activity in vivo and it is poorly absorbed when given orally, with resulting plasma levels less than 10 ng/ml in humans given 4 g/day [8,9].

Bromelain and immunomodulation

Bromelain is an immunomodulator with a pleiotropic effect [10]. It has been found to strengthen immunogenicity by increasing IFN-gamma and TNF alpha levels, significantly when the immune system is weakened [11]. In other studies, it has been reported that it inhibits mitogenesis, apoptosis and cytokine formation by preventing T cell activation in cases of inflammation, by blocking the Raf - 1/extracellular-regulated kinase (ERK)-2 pathway, through the reduction of CD4+ and CD25 expression [12,13].

In the studies conducted to date, through the CD4 and CD8 proteins in T cells of SARS-CoV-2 infection, interferon-gamma (IFN IL), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), nuclear factor kappa B (NF-κB) and tumour necrosis factor-α (TNF-α) have been found to increase the expression of cytokines [14,15]. Therefore, increased cytokine expression and the resulting tissue damage in COVID-19 is highly significant [16,17]. Thus, modulating cytokine levels both before and during the disease is the most critical way to combat COVID-19 infections [18-20].

The protective properties of bromelain have been demonstrated in both clinical and experimental inflammation models. It has achieved protective effects with its immunomodulatory, anti-oxidant and anti-inflammatory properties [21]. Therefore, it is likely that it may have a

protective effect against free oxygen radicals and inflammatory cytokines, especially during COVID-19 infections (Figure 1). It has been reported that it may exert a protective effect through the inhibition of T cells-mediated IL-6 and TNF-α, an particularly during the cytokine storm seen in COVID-19 patients [22]. The various beneficial effects of bromelain which minimize tissue damage during viral infections suggest that it could play a supportive therapeutic role in treatment of COVID-19 infection. Slowing the onset of inflammation will also prevent the disease from escalating.

Bromelain and its anticoagulant effect

It has been reported that cytokines cause thrombosis by increasing platelet aggregation [23]. Bromelain inhibits platelet aggregation due to its suppression of proinflammatory cytokines [24]. It has been shown to suppress kinins synthesis during inflammation [13]. This is particularly important for increased quinine levels during COVID-19. Because kinins are effective in both inflammation and coagulation, where they have an important role in multiple organ damage during COVID-19 infections. Thus, it is possible that bromelain, with its anti-inflammatory and anticoagulant effect, can prevent multiple organ damage through its suppression of the increased quinine synthesis during COVID-19 infections.

Bromelain has plasminogen-plasmin mediated fibrinolytic effect [25]. It has been shown to prevent thrombosis by inhibiting platelet aggregation, primarily by increasing the plasmin concentration. Thrombosis and coagulation are important for ventilation and during COVID infections it causes respiratory problems in patients by reducing erythrocyte transport, [23].

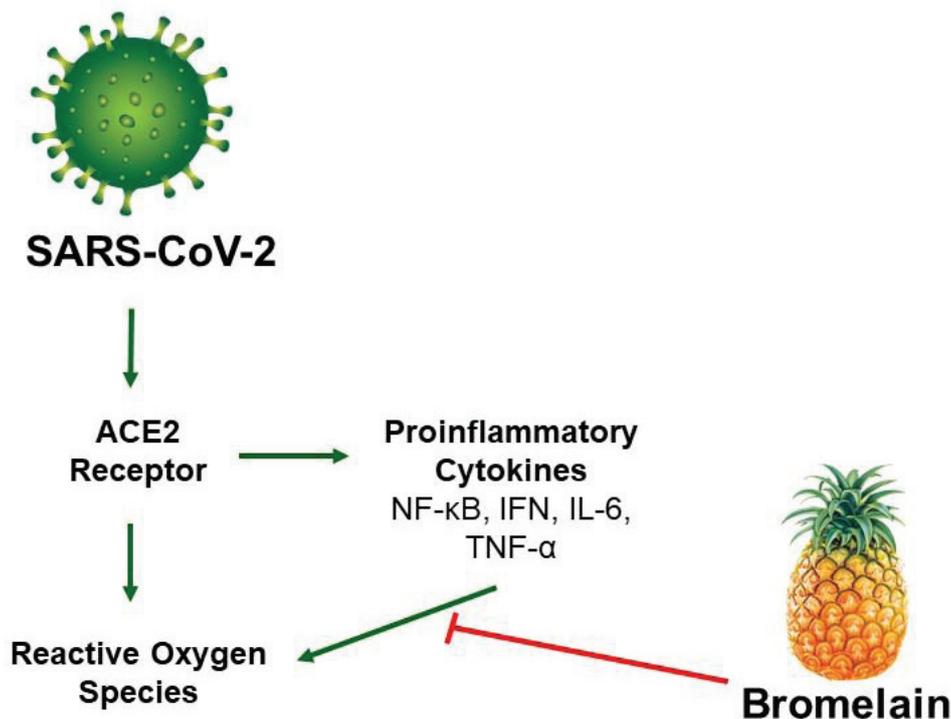


Figure 1: SARS-CoV-2 causes tissue damage by increasing proinflammatory cytokines and reactive oxygen species. Bromelain administration may ameliorate tissue damage by decreasing cytokine levels as well as reactive oxygen species.

Therefore, bromelain treatment is also important in terms of preventing coagulation and reducing respiratory distress.

Bromelain and neuroprotective effect

The analgesic and neuroprotective effects of bromelain are known [26]. The neurological symptoms of COVID-19 include headache, fever and fatigue [27]. Bromelain inhibits both kinins and PGE₂ which is likely to improve these symptoms. Additionally, it has been reported that bromelain enables the anti-oxidant/oxidant balance to be realized in favour of the anti-oxidant by stimulating endogenous anti-oxidants and decreasing oxidants [26]. Hence, bromelain can limit tissue damage during COVID-19. Although there are limited number of studies related to bromelain's antiviral effect, it can create a synergy with the adverse effects of additional antiviral drugs through its anti-oxidant and anti-inflammatory properties [21].

Conclusion

Bromelain, a phytotherapeutic drug and a crude proteolytic enzyme extracted from the pineapple plant with numerous beneficial properties [25], these include: preventing oedema formation, reduction of already-existing oedema in patients, anti-inflammatory and immunomodulatory effects [21,28,29]. Bromelain also contains different but closely-related proteinases that exerts anti-oedematous, fibrinolytic, anti-invasive, and antithrombotic activities [25,30]. Enzyme extracts of bromelain modulate the functions of adhesion molecules on blood and endothelial cells, and also regulate and activate various immune cells and their cytokine production [25].

COVID-19 is a serious viral disease that can lead to multiorgan failure and subsequent death through the disrupting effects of oxidant damage, cytokine storm and coagulation factors caused by the SARS-COV-2 virus. We suggest that in COVID-19 infection cases bromelain may reduce mortality and morbidity rates with its anti-oxidant, anti-inflammatory, immunomodulator and anticoagulant effects. Additionally, we propose that its use in combination with antiviral drugs in future clinical studies may decrease its negative side effects of the treatment.

Author contributions

S. Sayiner, A. Velioglu-Ögünç and A. Ö. Şehirli had the idea for the article, performed literature search and data analysis. S. Sayiner and A. Velioglu-Ögünç drafted the article and A. Ö. Şehirli critically revised the article.

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