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*Review Article*

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

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**Summary:** 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 disease. 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.

**Keywords***: Anticoagulant; Bromelain; Covid-19; Inflammation; SARS-COV-2*

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## INTRODUCTION

The sudden emergence of severe cases of pneumonia with an unknown etiological cause that was later identified to be a novel coronavirus was reported in late 2019 at Wuhan province of China. The disease caused by this novel coronavirus was later labeled as Coronavirus 2019 (CoVID-19) by the World Health Organization (WHO) on the 11th of February, 2020. This novel coronavirus is highly contagious and the disease spread like wildfire around the world, currently affecting more than five million people with over one thousand and three death worldwide.

CoVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus – 2 (SARS-CoV-2) which belongs to the β-coronavirus subtype. It is a single RNA positive strand of size 26 - 32 kbs in length and a diameter of 65 – 125 nm (Adnan *et al*., 2020). It belongs to the same class of deadly viruses, SARS-Cov and the Middle East Acute Respiratory Syndrome Coronavirus (MERS-CoV) which causes severe types of lower respiratory tract infection and acute respiratory distress syndromes (ARDS). They all belong to the family of Coronaviridae order Nidovirales. The emergence of coronavirus was first noticed in 2002 when there was a SARS-CoV outbreak that infected more than 8000 in 37 countries and causing 774 fatalities. Another wave of coronavirus pandemic occurred in 2012 caused by MERS-CoV which infected 2494 individuals and led to 858 deaths (Lu *et al*., 2020; Wit *et al*., 2016).

## STRUCTURE OF SARS-COV-2

SARS-CoV-2 is less than 80% nucleotide identical and 89.1% nucleotide similarity to SARS-CoV genes (Tao *et al*., 2020; Zhou *et al*., 2020). It possesses two untranslated regions (5' cap structure and 3'-poly-A-tail) and a single open reading frame (ORF) that encodes some polyprotein (fig. 1a) (Ge *et al*., 2020). The complete genome of SARS-CoV-2 contain replicate complex (ORF-1a and ORF-1b) encoding the non-structural protein (NSPs); spike protein (S) gene, an envelope protein (E) gene, membrane protein (M) gene, and nucleocapsid protein (N) gene all of which encode structural protein; accessory protein gene (ORF 3a, 7 and 8) that were inserted in the gees of structural proteins (Chan *et al*., 2020; Lu *et al*., 2020; Paraskevis *et al*., 2020); and several other unidentified non-structural open reading frames (ul Qamar *et al*., 2020). Spike protein gene is made up of two major subunits (S1 and S2 subunits) which are critical to the survival of the virus in the infected host. S1 subunit comprises of N-terminal domain and receptor-binding domain (RBD) used in forming a strong bond with the receptor of the host cell.

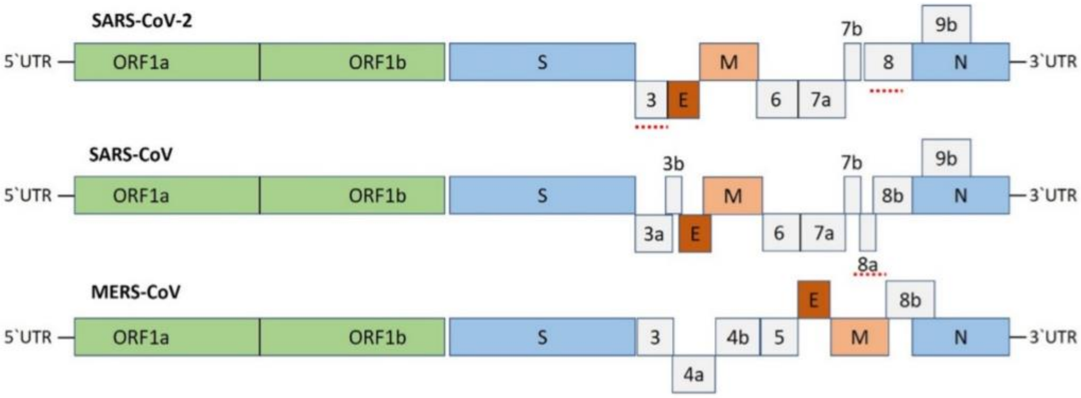


**Figure 1:**
Complete genomic sequencing of SARS-COV-2. (Adapted from Shereen *et al*., 2020).

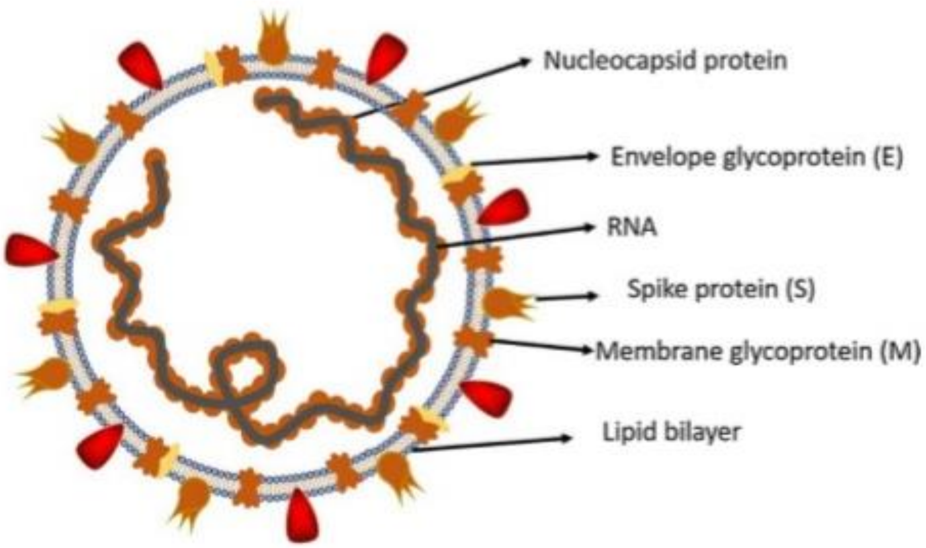


**Figure 2:**
Structure of SARS-COV-2 (Adapted from Shereen *et al*., 2020).

S2 subunit contains three functional domains (fusion peptide, heptad repeat-1, and heptad repeat-2) which change conformation to aid the fusion of the virus to the host cell membrane (Ge *et al*., 2020).

**TRANSMISSION of SARS-COV-2**

CoVID-19 is transmitted mainly through droplets, human-human close contact, and aerosol via self-inoculation of the mucus membrane of the eyes, nose, and mouth. SARS-CoV-2 has been detected in the tears, conjunctiva secretion, saliva, urine, and stool of the infected patient (Wang *et al*., 2020; Xia *et al*., 2020; Xiao *et al*., 2020). SARS-CoV-2 can survive on an inanimate material for up to nine days. Temperature ranges from 30 – 40 $^{0}$C has been said to reduce the survival of SARS-CoV-2 while the temperature of 4 $^{0}$C or below increases its persistence (Kampf *et al*., 2020).

SARS-CoV-2 infects the host cells by binding to the angiotensin-converting enzyme-2 (ACE-2) which is widely expressed in the cell membrane of the heart, kidney, lungs, gastrointestinal tract (GIT), brain, and liver. ACE-2 has also been found to be expressed in the eyes, nostrils membrane lining, and mouth. SARS-CoV-2 uses 394 glutamine residue in the RBD of the S1 motif which is recognized by the lysine-31 residue on the ACE-2 to establish a binding with the host cells while the S2 motif of the virus fuses firmly with the cell membrane (Adnan *et al*., 2020). Some cellular proteases such as furin, human airway trypsin-like protease (HAT) cathepsin, and transmembrane protease serine-2 (TMPRSS2) mediate proteolytic processes that aid penetration of the viral RNA into the host cell through the splitting of the spike protein (Bertram *et al*., 2011; Glowacka *et al*., 2011; Rizzo *et al*., 2020). In the infected cell, 3-chymotrypsin-like protease enzymes regulate the viral replication and it is essential for the life cycle.

**ORIGIN AND EPIDEMIOLOGICAL STUDY**

SARS-CoV-2 has been presumed to originate from the human seafood in the Wuhan market, China. Genomic evidence has shown that full genome sequencing of SARS-CoV-2 is 96% march of that of bat SARS-CoV (L. Wang *et al*., 2020). This finding suggested that SARS-CoV-2 may be of a zoonotic source having bat as a potential reservoir with intermediate host yet to be ascertained.

CoVID-19 is the third wave of a pandemic caused by coronavirus named SARS-CoV-2. After its emergence in China in 2019, it quickly spread around the globe from Asia to Europe, America, Australia, and Africa. It has infected over five million individuals with more than three thousand mortality. Elderly people and people with predisposing underlying health conditions such as diabetics, heart diseases, hypertension, etc. are 10 times more susceptible to viral infection. CoVID-19 infects the male gender more than females. This may be due to the large expression of ACE2 in males more than females (Sama *et al*., 2020). As at the time of this review, a total of 63,293 cases of coronavirus have been recorded in Africa with 2,290 fatalities. Nigeria has 4399 cases of CoVID-19 with 143 death across the country; South Africa has 10,015 cases, Egypt have 9400 cases, Morocco with 6063 cases, Algeria with 5723 cases, and Sudan with 1365 cases. Lesotho is the only African country that is yet to record any cases of CoVID-19. A study from China showed that the median age of patients infected by CoVID-19 is 47 years of which 87% of cases were in the age range of 30-79 years.

## COVID-19 MANIFESTATION

CoVID-19 incubation period in an infected patient ranges from 0 – 24 days with 14 days median time from the symptom onset to death. Individuals with CoVID-19 are best diagnosed by using reverse transcription-polymerase chain reaction (RT-PCR) techniques that perform genomic sequencing and matching it with the SARS-CoV-2 genome. RT-PCR is highly specific but low sensitivity test range of 60-80%, hence, repeated RT-PCR test is recommended for all negative results with a testing window of 24 - 72 hours. A study from China showed that 81% of patients have mild symptoms, 14% were severe while 5% were said to be in critical condition. Most symptoms of CoVID-19 were fever (87.9%), cough (67.7%), fatigue (38.1%) diarrhea (3.7%), and vomiting (5%) (Wang *et al*., 2020). Studies have shown that CoVID-19 affects various organs such as lungs, heart, liver, kidney, central nervous system (CNS), eyes, and gastrointestinal system either directly or as a comorbidity symptom. Cytokine storm, inflammation, pneumonia, and disseminated intravascular coagulation (DIC) have been highlighted as the major complications which lead to multi-organ failure in CoVID-19 patients.

## COVID-19 AND INFLAMMATION

One of the major pathophysiological events in CoVID-19 patients is the development of inflammation. The entrance of SARS-CoV-2 into the host cells leads to the massive activation of both neutrophils, dendritic cells, and macrophages which are mobilized to the site of infection. This first line of defense cells increases the production of chemokines and cytokines that promote the onset of inflammation. The resulting cytokines release syndrome is one of the critical factors that aggravate the disease progression and the major complications that result afterward. Interleukins (IL) – 6, IL-1, IL-2, IL-7, IL-10, and TNF-α are the resulting cytokine storms that are released in CoVID-19 patients. Chemokines such as Granulocyte Colony Stimulating Factor, 10 kD Interferon-gamma-induced-protein-10, Monocyte Chemoattractant Protein-1, and Macrophage Inflammatory Protein 1-α have also been reported to be elevated in the plasma of CoVID-19 patients.

Likewise, an increase in replication of SARS-CoV-2 has been linked with reduced interferon secretion. Low level of CD4+T and CD8 +T in most patients account for the imbalance between the type 1 and type 2 T-helper (Th) cells resulting in cytokines storm (Rizzo *et al*., 2020; Wang *et al*., 2020). A study from Chinese laboratory showed that Th1/Th17 promotes IL-6 in patients with CoVID-19 pneumonia (Rizzo *et al*., 2020). IL-6 has been tagged as the predictor of mortality in CoVID-19 Patients. In patients with mild symptoms, the IL-6 level is moderately increased and it reaches up to 25.2pg/ml in patients with a severe form of the illness (Hughes, 2008). The vital overall effect of cytokine storm is increased risk of vascular hyperpermeability, multiorgan failure, and eventually death.

Increased cytokines level has been linked with the activation of the coagulation pathway resulting in multiorgan failure. Studies have shown that the disseminated intravascular coagulation resulting from increased activation of thrombin is a major cause of mortality in CoVID-19 patients. Increased proinflammatory secretion causes impairment of Thrombin regulator (antithrombin III, tissue factor pathway inhibitor, and protein C system) which were evidence in severe CoVID-19 patient. Prevalent pulmonary embolism and venous thromboembolism aggravating ventilation-perfusion mismatch have been observed in CoVID-19 patients.

## COVID-19 AND RESPIRATORY SYSTEM

SARS-CoV-2 causes havoc on the lower respiratory tract. One of the major complications of CoVID-19 is the development of acute respiratory distress syndrome which usually occurs on the 9$^{th}$ day starting from the onset of symptoms in the severe patient (Huang *et al*., 2020). Studies have revealed that SARS-

CoV-2 primarily attacks the pneumocyte type II cell of the alveoli which form 83% of the apical epithelial cells (Li, 2020; Xu *et al*., 2020). Replication of SARS-CoV-2 in the cytoplasm of a pneumocyte induces oxidative stress which results in apoptosis of the apical cells. The cumulative effect of this includes the destruction of the alveoli capillary walls, predominant ground-glass opacity, irregular interlobular septal thickening, air bronchogram, and inflammation of the alveoli (L. Wang *et al*., 2020). These are the typical features of CoVID-19 pneumonia.

**COVID-19 AND CARDIOVASCULAR SYSTEM**

The devastating effect of SARS-CoV-2 on patients does not exempt the cardiovascular system. Due to the high expression of ACE2 in the heart, various degrees of damaging effects have been recorded on the cardiovascular system. Patients with CoVID-19 have been reported with heart arrhythmia, acute heart injury, lymphopenia, and thrombocytopenia (Wang *et al*., 2020). Few reported cases of leukopenia (33.7%) as well as thromboembolism have been noted. Myocarditis, cardiac arrest, and acute heart failure are common symptoms displayed in about 40% of CoVID-19 patients (Chen *et al*., 2020). It is however not ascertained whether cardiovascular diseases are directly provoked by SARS-CoV-2 or are its comorbid effects due to increased cardiometabolic demand. An insinuation that patients under the treatment of angiotensin II receptor blocker (ARB) may be highly susceptible to CoVID-19 has been soundly disproved by some studies that show a lack of linkage with such treatment (Ferrari *et al*., 2020; Sama *et al*., 2020). Likewise, it has been shown that ARB does not increase ACE2 level and hypertension does not increase CoVID-19 infection. It has been strongly recommended that CoVID-19 patients should be on the watch out for the development of cardiovascular heart disease as baseline comorbidity and as a complication.

**COVID-19 AND THE NERVOUS SYSTEM**

COVID-19 has generally been studied for common symptoms, hence limited studies have reported its neurological effect on patients. A study from China reported that 36.4% of COVID-19 patients showed neurological manifestation (Mao *et al*., 2020). ACE2 is expressed in the central nervous system as well as the ocular tissues. SARS-CoV-2 certainly, finds its way to the nervous system to produce damages due to its neuroinvasive capabilities. It possibly spreads from the respiratory tract to the CNS. SARS-CoV-2 has been found in the cerebrospinal fluid (CSF), tears, and conjunctiva secretion. It can also gain access to the CNS through the olfactory bulb to cause neuroinflammation and demyelination of central neurons (Bohmwald *et al*., 2018). CoVID-19 patients generally complain of fever, body weakness, fatigue, ocular surface infection, headache, body pain, and some degree of dyspnea (Asadi-Pooya & Simani, 2020). Febrile seizures, convulsion, encephalitis, and changes in mental status have also been reported in some patients (Bohmwald *et al*., 2018; Desforges *et al*., 2019).

**HERBAL MEDICINES AND COVID-19**

The use of traditional herbal medicine as an antiviral remedy started since the emergence of CoVID-19 (Yang *et al*., 2020). The different continental regions have produced herbal concoctions projected for the treatment of CoVID-19. Chinese traditional medicines have been promising in the treatment of CoVID-19, their antiviral effects have been evaluated on SARS-CoV-2 infection in both humans and mice (Luo *et al*., 2020; Yang *et al*., 2020). In particular, Shuanghuanglia oral liquid has been claimed to inhibit the growth of SARS-CoV-2 (Wang *et al*., 2020). Its effects have been linked with its anti-inflammatory properties that significantly reduce inflammatory responses of the body in the course of progression of the infection (Wang *et al*., 2020). In Africa, Madagascar herbal concoction (CoVID-Organics) has been trending because of the claim of its antiviral effect on SARS-CoV-2. Currently, the CoVID-Organics has been distributed around various African countries for more clinical trials.

**BROMELAIN**

Bromelain is a major cysteine endopeptidase protease inhibitor found in the family of Bromeliaceae of which pineapple is the most popular. Pineapple is a native of South America but it is now widely grown in various parts of the world including Africa. Bromelain contains numerous cysteine proteinase that are closely related but different amino acid sequencing, specificity as well as sensitivity to inactivation. It contains peroxidase, acid phosphatase, several protease inhibitors, and organically-bound calcium. It is made up of 212 amino acids and the molecular weight is 33 kDa (Gautam *et al*., 2010).

Bromelain is classified into stem and fruit bromelain based on the part of the plant it was extracted from. Stem bromelain (EC 3.4.22.32) is the most abundant proteinase derived from pineapple. It is different in specificity compared with fruit bromelain (EC 3.4.22.33) and cleaves preferentially into the Z-Arg-Arg model substrate whereas fruit bromelain cleaves into Bz-Phe—Val-Arg (Napper *et al*., 1994). Stem bromelain has been reported to contain 285 amino acids of which alanine and glycine are the most abundant, while histidine and methionine are present in minute quantity.

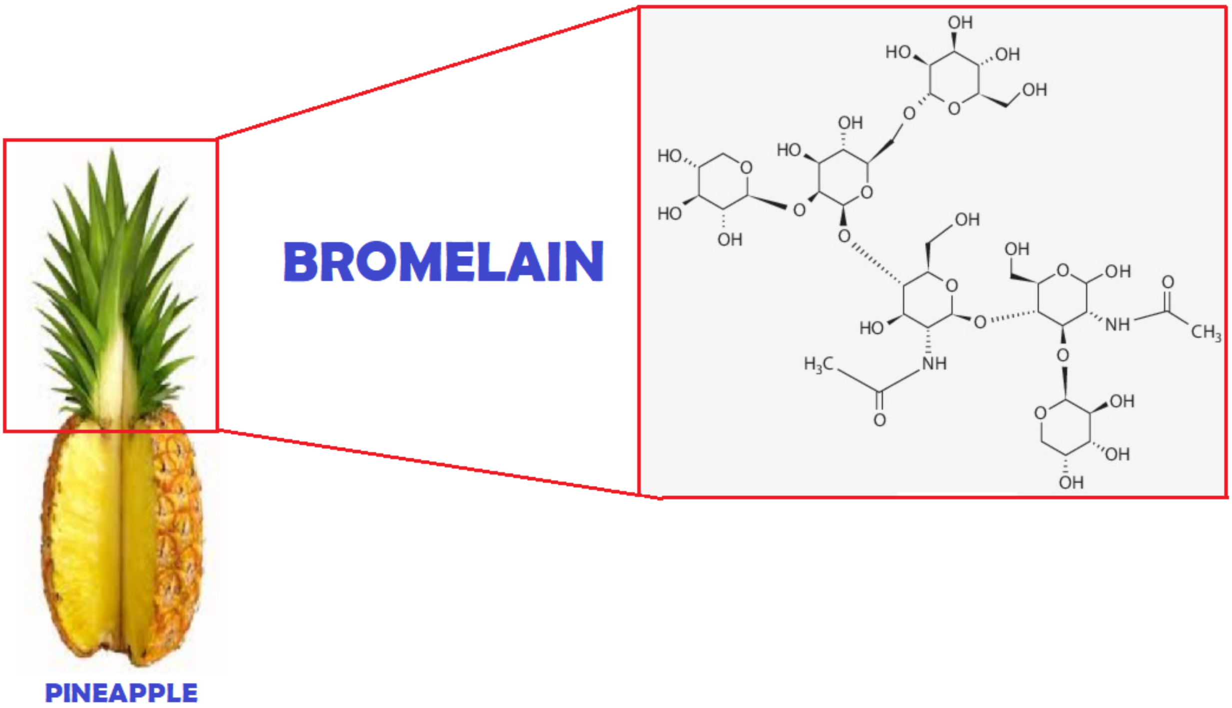


**Figure 3:**
Molecular structure of bromelain from pineapple stem

Stem bromelain also contains four hexosamines, and 2.1% carbohydrate, meaning it is a glycoprotein. The carbohydrate composition in stem bromelain consists of mannose, fructose, xylose, and glucosamine in the ratio of 3:1:1:4 using gas chromatography analysis (Benucci *et al*., 2011).

The molecular weight of purified stem bromelain is between 23.40 to 35.73 kDa, while fruit bromelain is 31.00 kDa. Bromelain is stable at pH 3.0 - 7.5 and once it has combined with its substrate, the activity is no longer susceptible to the effect of the pH (Grzonka *et al*., 2007). Bromelain is well absorbed from the GIT in a functionally intact form (Babagana & Bala, 2016).

## THERAPEUTIC BENEFITS OF BROMELAIN

Bromelain has been widely used for the treatment of numerous pathological conditions which include inflammation, cancer, wounds, analgesic, GIT disorder, microbial infections, and as an anti-oxidant. Both experimental and clinical tests have confirmed the bioactivities of bromelain in *in-vivo* and *in-vitro* studies.

**Anti-viral effects:** Few studies have reported the antiviral effect of bromelain. Clinical study on acquired immune deficiency syndrome (AIDS) caused by Human immunodeficiency virus (HIV), cervical cancer caused by Human papillomavirus, and hepatitis C patients showed that bromelain substantially increases CD4+ T-cells count (Suthihono *et al*., 2011). A study involving seven HIV infected patients showed that after four months of treatment with pineapple juice, three patients had normal CD4+ T-cells count while two showed low viral count below the detection limit (400 copies/ml) (Maruli *et al*., 2014). An in-vitro study showed that bromelain (10 mg/ml, specific activity of 5.88 U/mg) could kill HIV (Suthihono *et al*., 2011). Bromelain has also been shown to be effective against poliovirus 1 (Comosus & Peel, 2013). More experimental studies are required to ascertain its actual potency and effectiveness.

**Anti-inflammatory effects:** Clinical and experimental studies have shown that bromelain possesses anti-inflammatory activities (Hale *et al*., 2005; Rathnavelu *et al*., 2016). Bromelain acts as a modulatory agent of cytokines. It can stimulate the release of proinflammatory cytokines in a healthy immune system in response to cellular stress (Barth *et al*., 2005). It increases the release of IL-1β, IL-6, interferon-γ (INT-γ) and TNF-α in mouse macrophages and human peripheral blood mononuclear cells (Rathnavelu *et al*., 2016). Conversely, bromelain inhibits the biosynthesis of pro-inflammatory cytokines and prostaglandins under inflammatory conditions induced by overproduction of cytokines (Onken *et al*., 2008). It reduces the expression of CD44 on the surface of immune cells that regulate lymphocyte homing and migration (Rathnavelu *et al*., 2016; Subramaniam *et al*., 2007). In our yet to be published data, it was found that bromelain inhibited brain and sciatic nerve cytokines and prostaglandin $E_2$ production in a peripheral model of neuropathic pain. It also showed that bromelain mitigated the activities of nuclear factor-kappa β (NF-κβ) which was significant for the production of proinflammatory cytokines (Bakare & Owoyele, 2019b). Bromelain also inhibited IL-1β, IL-6, and TNF-α in the cerebral cortex and sciatic nerve.

Likewise, Bhui and his colleagues reported that bromelain inhibited COX-2 expression in mouse skin tumorigenesis as well as upregulation of p53 and Bax. (Bhui *et al*., 2009). In their study, bromelain inhibited extracellular signal-regulated protein kinase (ERK ½), p38 mitogen-activated protein kinase (MAPK), Akt, and NF-κβ activities which are key cellular activities that enhance the production of proinflammatory cytokines that mediate inflammation and pain.

It has also been reported that bromelain ameliorated inflammation in the respiratory system (Jr *et al*., 2008). Studies showed that bromelain inhibited the infiltration of the lungs and airway by the eosinophils and leukocytes (Jr *et al*., 2008; Secor *et al*., 2005). In these studies, bromelain also modulated the activities of CD19+ B cells, and CD4+ and CD8+ T lymphocytes. The overall effect of these processes was inhibition of the development of bronchitis and respiratory distress syndrome and aiding of smooth breathing. Bromelain was also found to mitigate the development of allergic airway disease by modulating CD4+ to CD8+ T cells population (Pavan *et al*., 2012).

**Antinociceptive effects:** Experimental and clinical evidence showed that bromelain possesses analgesic properties. Bromelain has been constantly used as an analgesic agent for the treatment of arthritis pain, muscular pain, episiotomy pain, and perineal pain (Golezar, 2016; Majid & Al-mashhadani, 2014). It has also been reported that bromelain improves the quality of life and subsides pain after mandibular third molar surgery. Walker and his colleagues (Walker *et al*., 2002) reported bromelain to be dose-dependent in its effectiveness for subsiding mild knee pain.

Our study on the antinociceptive effect of bromelain in chronic constriction injury (CCI) model of neuropathic pain in Wistar rats showed that bromelain mitigated hyperalgesia and allodynia after twenty-one days of its administration (Bakare & Owoyele, 2020). In another study using CCI, bromelain was shown to regulate neuronal electrolytes ($Ca^{2+}$, $Na^{+}$, $K^{+}$, and $Cl^{-}$) imbalance as a mechanism of action (Bakare & Owoyele, 2019a). We also reported that bromelain serves as a good antioxidant that promotes the secretion of antioxidant enzymes (superoxide dismutase, catalase, and reduced glutathione) via increased Nuclear Factor Erythroid-Derived 2-Like 1 and 2 (NrF-1 and NrF-2) Concentration (Bakare & Owoyele, 2020). It mitigated the expression of nitric oxide synthase thereby inhibiting the production of nitric oxide and reactive nitrogen species.

**Anti-coagulating effects:** The anti-coagulation effect of bromelain in both *in-vivo* and *in-vitro* study have been documented in many studies. Bromelain inhibited platelet aggregation and improved ischemic/reperfusion dysfunction (Hilberg & Gla, 2006; Juhasz *et al*., 2008) and has been shown to prevent angina pectoris and transient ischemic attacks (Zengion *et al*., 2011). It prevented thrombosis formation, thrombophlebitis, and had fibrinolytic activities through increased secretion of plasmin (Errasti *et al*., 2016; Sudjarwo, 2005). It reduced the plasma kininogen level, thereby inhibiting kinins synthesis, swelling, and pains (Zengion *et al*., 2011). The overall effects of bromelain are the improvement in the cardiovascular and circulatory functions of the body system.

## COULD BROMELAIN BE USEFUL IN THE MANAGEMENT OF COVID-19?:

Currently, there is no designated drug for the treatment of CoVID-19. Anti-virals, antimicrobials, anti-inflammatory drugs, and some herbal mixtures have been put into trials to curb the progression of the viral infection (Adnan *et al*., 2020). All these drugs had limited success in curing the CoVID-19. Initially, treatment was focused on relieving CoVID-19 associated pneumonia which was one of the major complications of the infection (Jin *et al*., 2020; Shen *et al*., 2020). It was subsequently affirmed that cytokines storm that results in inflammation and disseminated intravascular coagulopathy were mainly responsible for multiorgan failure (Jose & Manuel, 2019). In the bid to combat CoVID-19, novel drug needs to be formulated that will inhibit the viral replications and mitigate the development of SARS-COV-2 pathophysiological reactions in the body system.

The Anti-inflammatory and anti-coagulatory capacity of bromelain has been wildly reported (Suthihono *et al*., 2011). Bromelain inhibits pro-inflammatory cytokines especially IL-6 and TNF-α which have been reported as the hallmark of cytokine storm in CoVID-19 patients (Kakodkar & Kaka, 2020). The various physiological effects of bromelain make it one of the potential candidate drugs that could be deployed for the treatment of symptoms of CoVID-19 infection. Slowing down the advent of inflammation will prevent escalation and the progression of the disease.

Cytokines have also been reported to aid platelet aggregation resulting in thrombosis (Jose & Manuel, 2019). The mitigating effect of bromelain on pro-inflammatory cytokines will inhibit this cascade of reaction that led to platelet aggregation (Errasti *et al*., 2016). The ability of bromelain to inhibit the biosynthesis of kinins that promote the development of inflammation will further prevent the advent of cytokines storms and systemic coagulation (Secor *et al*., 2005) which causes the multiorgan failure that characterizes CoVID-19 infection. Furthermore, bromelain has been documented to promote fibrinolysis through the plasminogen-plasmin system (Errasti *et al*., 2016). Bromelain inhibits platelet aggregation as well as increases plasmin concentration in the blood that prevents thrombosis. Thrombosis and coagulation reduces erythrocyte transportation and affects ventilation-perfusion rate in CoVID-19 patient which accounts for acute respiratory distress syndrome that the patients develop (Jose & Manuel, 2019). Treatment with bromelain may curb the coagulopathy by promoting the free flow of the blood around the circulating system.

Bromelain is a proven analgesic and neuroprotective agent (Bakare & Owoyele, 2020). CoVID-19 patients have reported experiencing headaches, fever, body weakness, and fatigue (L. Wang *et al*., 2020). Bromelain offers a wide window in abating such neurologic experience via inhibition of prostaglandins ($PGE_2$ in particular) and bradykinin which is a known mediator of headache and fever. Bromelain reduces oxidative stress in organs via inhibition of cellular peroxidation, nitric oxide synthase, and stimulation of antioxidant enzymes (Bakare & Owoyele, 2020).

Hence bioactivities of bromelain could limit the progression of CoVID-19. However, its combination with one or two antiviral drugs will make it more effective since the limited study has reported its antiviral activities (Suthihono *et al*., 2011). Remdesivir and/or its combination with hydroxychloroquine or other antiviral drugs has yielded the most promising results in infected patients (M. Wang *et al*., 2020). On the other hand, limited study has been conducted on the antiviral effects of bromelain. Its combination with remdesivir or other antiviral drugs may prove effective in curbing CoVID-19 infection in patients.

In conclusion, CoVID-19 is a severe viral disease caused by the SARS-COV-2 virus which results in multiorgan failure and subsequent death. Bromelain shows a lot of potentials that make it a possible candidate for the treatment of symptoms of CoVID-19 infection. Its combination with remdesivir or other anti-viral drugs may provide a golden solution to eradicate the CoVID-19 pandemic. Further research in these directions may yield a lot of dividends.

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