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REVIEW

Bromelain, a Potential Therapeutic Compound from *Ananas Comosus*

Ananas Comosus (Bromeliaceae) Bitkisinden Elde Edilen Potensiyel Terapötik Etkili Bileşik Bromelain ve COVID-19 Üzerine Yapılan Çalışmalar

Aydın Alper Şahin

Department of Pharmaceutical Product, Certification Unit, Turkish Medicine and Medical Devices Agency, Ankara, Turkey

Abstract

Bromelain is a mixture of enzymes found in crude extract from the fruit and other parts of the pineapple *Ananas comosus* (Linn.), Bromeliaceae family. Bromelain is a nontoxic compound having various industrial and therapeutic applications. It consists of varied closely related proteinases that are important as anti-inflammatory, antithrombotic, and fibrinolytic agents. Bromelain is widely administered for its well-known properties, such as anticancer activity, antioxidant activity, and immunomodulatory effects. It also plays a major role in the modulation of the immune system and prevents the harmful effects of the cytokine storm. Because of all these therapeutic effects, bromelain appears to be a potential candidate to inhibit and prevent the symptoms of different diseases as well being an effective, natural, therapeutic weapon for the treatment of severe COVID-19 infection.

Keywords: Bromelain; Enzymes; COVID-19

Pineapple, *Ananas comosus*, has been used as part of traditional folk medicine since ancient times. It continues to be present in various herbal preparations. This plant, first seen by Columbus and his crew in the Caribbean islands in 1493, is native to South America and was introduced to Europe by Spanish explorers with the discovery of America. The pineapple was brought to England in 1660 and it has been grown commercially in greenhouses and in many fields since the 1820s. When European explorers discovered this tropical fruit in the Americas, they called it "pineapples." The original name of the fruit comes from the word nanas, which means "excellent fruit." Pineapple is substantially produced because of its fruit which bears good taste and flavor.[1] Pineapple is also popularly used in different cuisines and by the food industry. However, this fruit is used in different fields, such as medical, cosmetic, or industrial applications as well as food. While Hawaii, Costa Rica, Brazil, Thailand, and the Philippines were the leading countries in pineapple production for a long time, today the plant can be grown in different geographical locations.[2]

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Correspondence: Aydın Alper Şahin, M.D. Türkiye İlaç ve Tıbbi Cihaz Kurumu, Farmasötik Ürün Sertifikalandırma Birimi, Ankara, Turkey
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Ananas is a perennial herbaceous plant species belonging to the Bromeliaceae family. It is a plant that can grow up to 1–1.5 meters in length and varies in width and height. *A. comosus* has a spiral morphology due to the arrangement of the leaves, and has a short, sturdy stem. The flowering period of the plant varies between 15–30 days.[3]

Phytochemistry of *A. Comosus*

The plant contains proteins, carbohydrates, and some compounds like alkaloids, flavonoids, phenolic compounds, saponins steroids, and terpenoids.[4]

The plant and fresh pineapple fruit are very rich in vitamins, like retinol, folic acid, pyridoxine, thiamine, pantothenic acid, riboflavin, and ascorbic acid as well as in some minerals, such as manganese, calcium, zinc, copper, and iron. Pineapple consists of 80%–85% water whereas total solids are 13%–15%. The solid part is around 85% carbohydrates, mostly monosaccharides (glucose, sucrose, fructose, etc.), with the remaining other nutrients.[5] The fruits contain some organic acids, such as tartaric and malic acids and fats with fiber as well some amino acids as follows: glutamic acid, glycine, alanine, leucine, isoleucine, and histidine.[6]

Additionally, that the flavonoid myrcetin, and phenolic acids, such as p-hydroxybenzoic, syringic, tannic, sinapic, caffeic, trans-cinnamic, and salicylic acids, were also reported to be obtained from the fresh fruit of *A. comosus*.[7]

The other substances, such as Z)-3-hexen-1-ol, methyl octanoate, 2-phenyl-1-ethanol, 2-methyl-3-buten-2-ol, and 1-hexanol, and some of the various volatile substances, such as acetic acid, 5 hydroxymethyl furfural, formaldehyde, 2-methyl-3-buten-2-ol, methyl pentanoate, linalool, and hexalactone have been obtained from Ananas juice and fruit.[8,9]

Bromelain from Pineapple

One of the major components of pineapple is bromelain, which was identified in the late 19th century. The highest concentration of bromelain is found in ripe pineapple fruit pulp and in the stems. The proteolytic fraction of pineapple stem is termed stem bromelain, while the one presents in the fruit is known as fruit bromelain. The therapeutical potential of bromelain was revealed in 1950s. Despite being found in all parts of the pineapple, extracts from the seeds are commercially preferred. Bromelain belongs to the protein digestive enzyme group and includes thiolendopeptidases and other enzymes, phosphatases, glucosidases, peroxidases, cellulases, and escharase. It also contains glycosidase-like components, carbohydrates, glycoproteins, and several protease inhibitors. Bromelain has cysteine proteinases that have different proteolytic activities. According to biochemical studies, crude bromelain consists of different closely related proteinases and the complex of proteolytic enzymes also contains sulfhydryl proteases. [10,11]

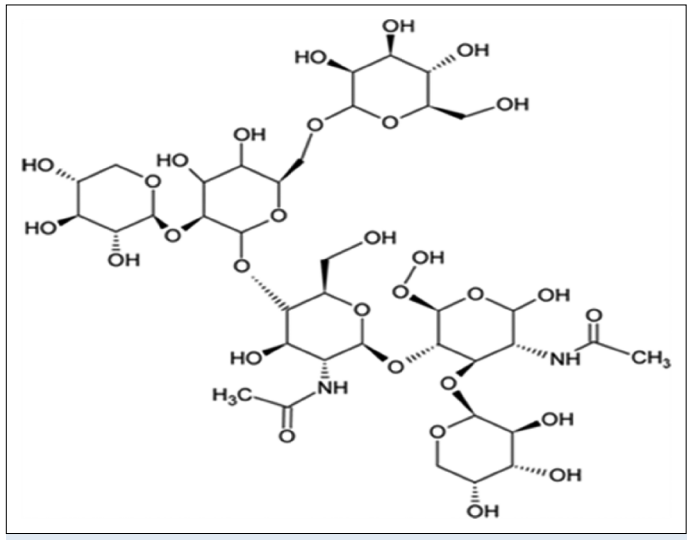

Figure 1. The chemical structure of bromelain from pineapple juice.[12]

The potential therapeutic value of bromelain comes from its biochemical and pharmacological properties and the structure of bromelain is shown in Figure 1.[12]

Bromelain exerts its activity over a pH range of 4.5–9.5. Different methods have been used to investigate pure bromelain. Today, it is generally obtained from pineapple juice and fruit using centrifugation techniques, ion exchange and other various chromatographic methods, ultrafiltration, and lyophilization processes.[13,14]

The pineapple fruit is widely used as a food source; thus, the main extraction source of bromelain is usually the stem of the pineapple plant, which is a cheaper source as it is the inedible part of the plant.

Pharmacological Effects of Bromelain

Anticoagulating Effect

Coagulation is also known as clotting. It is the process by which blood changes from a liquid to a gel, forming a blood clot. The coagulation system is a chain of sequential reactions in which coagulation factors activate each other. The coagulation process is classically initiated by both extrinsic (external) and intrinsic (internal) ways. These pathways play a vital role in preventing blood loss by forming clots. However, in certain pathological conditions, these clotting factors can cause serious problems in individuals, leading to fatal diseases. The anticoagulant effect of bromelain from pineapple was first described in 1972 when it showed an

anticoagulant effect in 17 out of 20 volunteers after oral administration.[2] Bromelain increased the blood clotting time and inhibits platelet aggregation In one study, bromelain also increased activated partial thromboplastin and prothrombin time. With the help of these studies, it was thought that bromelain could break down cholesterol plaques as well it has strong fibrinolytic effect.[15,16]

Cardiovascular Effect

Among cardiovascular diseases are blood vessel and heart conditions, heart attacks, cerebrovascular disease, hypertension, peripheral arterial disease, rheumatic heart disease, and congenital heart disease. Stroke and heart disease are the leading causes of death. Angina pectoris and ischemic attacks are fatal complications that result from impaired blood flow to the heart due to thrombus formation. *In vitro* and *in vivo* analyses have shown that bromelain administration prevents aggregation of human blood platelets and minimizes the severity of angina pectoris and transient ischemic attacks. Oral administration of bromelain in doses ranging from 400 mg to 1 g in a group of patients with angina pectoris was found to relieve all symptoms. In thrombophlebitis, a blood clot blocks blood flow veins. However, it has been found that the mechanism of bromelain is through elimination of clots by interfering with fibrinogen, thereby facilitating free blood flow through blood vessels.[10,17,18] Bromelain has also been noted to increase aortic flow and reduce infarct size and risk of death.[8,19]

Antiosteoarthritis Effect

Osteoarthritis is known as joint pain disease. It is a degenerative disorder. Patients limit their activities due to severe pain. In a study, the analgesic effect of bromelain was compared with those of known analgesics, such as diclofenac, naproxen, and ibuprofen; bromelain administration resulted in significant decrease in pain and knee stiffness in patients. Treatment with bromelain combined with cyclosporine reduced destructive arthritis and inflammation. Bromelain can be offered as an alternative to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). Bromelain reduces pain by acting on pain receptors, such as bradykinin.[20]

Antidiarrheic Effect

Some pathogens, such as *Escherichia coli* and *Vibrio cholera*, cause diarrhea through their endotoxins. Bromelain has been found to oppose the action of these endotoxins.; it exerts this effect by interacting with intestinal secretory enzymes According to another study, bromelain exerts its effects by inhibiting the adhesion of *E. coli* to glycoprotein receptors on the intestinal surface, known as the antiadhesion effect.[5,21] Bromelain has also been successfully used to treat ulcerative colitis, with patients' symptoms improving rapidly. Apart from the prevention of intestinal disorders, bromelain has been successfully applied to treat exocrine pancreatic insufficiency.[21,22]

Anticancer Effect

When the human body regulates cell proliferation and growth, cell cycle disparities can lead to the corruption cell growth and turn a normal cell into a cancerous cell. However, various mechanisms in the human cells protect DNA from harmful genomic differentiation and toxins.[23,24] Though different pathways lead to the proliferation and metastasis of cancerous cells, inflammation is one of the major factors in the development of cancer during cellular transformation, angiogenesis, proliferation, metastasis, and invasion. Bromelain has been found to interfere with these pathways, that leads to malignation. Bromelain increases the effects of chemotherapeutic agents. Bromelain has been found to be very effective in reducing the number of mice's skin papilloma cells, gastric carcinoma cells, and glioblastoma cells. The inhibitory effects of bromelain on neoplastic cell proliferation have been widely documented for various human neoplasms such as leukemia, lymphoma, melanoma, pulmonary carcinoma, gastrointestinal carcinoma, breast cancer and epidermoid carcinoma. The main mechanism of action in these studies was observed through the enhancement of apoptosis, known as programmed cell death.[23,24]

Melanoma and Epidermoid Carcinoma: Bromelain was found to have effective anticancer action against melanoma and epidermoid carcinoma. Bromelain dramatically decreased their proliferation and reduced COX-2 gene expression. In addition to this, bromelain also lowered the amount of CD44, which is a kind of protein found in human Molt 4/8 leukemia cells.[25]

Breast Cancer: Bromelain prevents the growth of MCF-7 cells and initiates the autophagy process induces cancer cell death through apoptosis. It also promotes monocytic cytotoxicity in breast cancer patients in oral use.[26]

Colorectal Cancer: Though Bromelain's colorectal cancer pathway has not been fully investigated, it has found in animal studies that bromelain suppresses cell growth and tumor formation. Therefore, bromelain applications in colorectal cancer are indicated to have better results than other well-known treatments.[27]

Hepatic and Pancreatic Cancer: It was shown that bromelain alone or in combination with N-acetyl cysteine is capable of inducing tumor regression in hepatic and pancreatic cancer. With the regular and simultaneous use of bromelain besides the current clinical chemotherapeutic dose planned to be administered, it was noted that the treatment process was significantly reduced.[28]

Effect on Prostate and Prostate Cancer: Prostate cancer was treated by using a combination of bromelain and cisplatin in addition to its observed properties, such as inhibiting cell proliferation, weakening invasiveness, and promoting apoptosis in neoplastic cells. Additionally, it was observed that a combination of bromelain, papain, and quercetin was used for one month in the treatment of a group of chronic prostate cancer patients and had got better results than the treatment already being applied.[29]

Recent studies have provided information that this enzyme stops lung metastasis. The presence of some proteins from bromelain that can also inhibit the development of a wide range of tumor cells which include melanoma, breast, lung, colon, and ovarian cancers. This indicates that bromelain can be used in a wide variety of cancer research and treatments, including its antitumor effect.[30]

Anti-inflammatory Effect

Inflammation is recognized as a complex biological mechanism primarily regulated by disruption of tissue homeostasis. By suppressing chronic inflammation, the incidence of cancer can be reduced, and the progression of cancer can be prevented.[31] Bromelain stimulates interleukin (IL)-1β, tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), and interferon (INF)-γ, which are considered inflammatory mediators in human peripheral blood mononuclear cells and mouse macrophages. In one study, Bromelain was shown to stimulate higher levels of T and B cells in mice and to act as a potent immunomodulatory agent that can help boost the immune system. In another study, it was reported that two ulcerative colitis patients became healthy after the administration of bromelain. Bromelain has also been shown to reduce the expression of TNF-α and INF-γ in inflammatory bowel disorders. In a murine model of acute asthma, bromelain reduced airway reactivity and sensitivity to irritants and markers of lung inflammation, including infiltration by eosinophils and leukocytes. Neuroinflammation alters the microenvironment in certain areas of the brain, leading to the development of Parkinson's disease. Mechanisms involving cytokine and non-cytokine-derived pathways are activated in the inflammatory response. Proinflammatory cytokines, interleukin-1 β (IL-1β), IL-6, and TNF-α were widely reported to mediate and facilitate both neural activities and inflammatory processes.[31,32]

Furthermore, bromelain modulates the expression of transforming growth factor-β, one of the major regulators of inflammation in patients affected by osteomyelofibrosis and rheumatoid arthritis. All these results suggest that a healthy immune system can potentially be achieved using bromelain.[33,34]

Antimicrobial Effect

V. cholerae and enterotoxigenic *E. coli* (ETEC) are two organisms that cause diarrhea. In a study, Bromelain inhibited ETEC receptor activity in the small intestine *in vivo* and protected animals from diarrhea and diarrhea-induced death. Bromelain prevented *E. coli*'s production of enterotoxin by destroying bacteria.[22,34] Bromelain can be used to destroy different pathogenic intestinal organisms. The synergistic effect of bromelain was also observed when used simultaneously with antibiotics. Therefore, bromelain was also used as a supportive treatment with trypsin and routine in the treatment of sepsis in children.[35]

Antioxidant Effect

Bromelain can act as an antioxidant. It also performs this activity as lipid peroxidation inhibition and free radical sweeper. Bromelain which shows similar effects as some antioxidant agents can reduce oxidative stress by ending the oxidative chain reaction that inhibits oxidative damage. Bromelain is stated to protect the human body from diseases caused by free radicals with little or no side effects at all.[36,37]

Immunological Effect

Since bromelain can both activate and suppress the immune system, it has been noted for its immunomodulatory effect in various epidemiological studies. Bromelain has been shown *in vitro* experiments to increase CD2-mediated activation of T cells and improve antigen-independent binding of T cells to splenocytes.[38,39] A study with bromelain and trypsin showed that, bromelain, but not trypsin, activates macrophages/monocytes and type 1 cells regardless of the underlying autoimmune disorder, namely encephalomyelitis disseminata (ED). Therefore, bromelain can stimulate the innate immune system as well as the adaptive immune system.[40]

Immunogenicity Effect

Bromelain not only can increase the binding of cell surface molecules to immune cells, such as T cells, natural killer cells, and macrophages, but also increases the secretion of IL-1, IL-6, and TNF-α. In autoimmune diseases, bromelain can reduce the activation of CD4 T cells (immune cells) and it suppresses immune activation.[41]

Other Pharmacological Effects

Effect of Bromelain on Contraction of The Uterine Muscles: During the last period of pregnancy, the hormone oxytocin is naturally released by the pituitary gland, which aids in uterine contraction. Many studies have been carried out to find natural or synthetic stimulants of the hormone oxytocin and to combat complications associated with childbirth.[22] For this purpose, the effect of pineapple on uterine contraction was investigated. In one study, the uterine muscles of rats were removed and their behaviors were studied by administering fresh pineapple juice with acetylcholine and different drugs such as atropine at the same time. Bromelain in pineapple caused uterine contraction just like acetylcholine. It has been stated that bromelain can cause contraction with agonistic activity on M2 and M3 muscarinic receptors.[42]

Antinociceptive Effect and Wound Treatment: Clinical and experimental evidence showed that bromelain has analgesic properties. Therefore, bromelain is used specifically to reduce pain and edema of the nose and sinuses. Bromelain educes swelling and bruising and shortens recovery time after injury and surgical procedures. It has been used to treat muscular and perineal pain and some study results have shown that regular intake of bromelain at 500 mg per day can be effective in reducing pain and can also accelerate wound healing. Bromelain reduces plasma kininogen, thereby inhibiting the production of kinin, which is known as an agent that causes inflammation, pain, and swelling. For that reason, researchers attach importance to its effectiveness in recovery after plastic surgery.[11,43] In dentistry, researchers evaluated the effect of oral bromelain administration (1000 mg/day) on postoperative pain in patients who had surgical extraction of impacted mandibular third molars and reported that bromelain significantly reduced pain and edema compared to placebo.[44] In further studies, it has been shown that when given in a daily dose of 1000 mg, bromelain can be used as a substitute for diclofenac in patients who do not tolerate it or for whom it is contraindicated. Bromelain can be used alone to manage postoperative pain and swelling that follows the mandibular molar surgery. As a conclusion of these studies, bromelain is not only effective to reduce the pain but also has fewer side effects compared to NSAIDs.[45,46]

Bromelain in Treatment of Burns: Removal of damaged tissue from wounds or second/third degree burns is called debridement. In general, debridement is a practice that helps improve wound healing. Tissue residue is precisely cleaned by the application of this process. If this procedure is not performed, the surface of the wound will not heal in a healthy way. By performing this, bacterial formation around the wound is also prevented. Bromelain has been used in gel and cream forms to treat burns and has been proven effective in treating wounds. When these preparations were applied, it was observed that bromelain treated the necrosed tissue without any side effects. It is stated that the enzyme "Escharase," which is found in bromelain, is responsible for this treatment. Escharase is not a proteolytic enzyme; it is known that it does not have hydrolytic enzyme activity against normal protein substrate or various glycosaminoglycan substrates. Enzymatic debridement made using bromelain are more preferred than painful surgical incision clutches. The reason is that it does not expose patients to repeat anesthesia and significant bleeding risk.[47]

Use of Bromelain in Dermatology: *Pityriasis lichenoides*, an idiopathic, chronically squamous skin disease in humans, can be effectively cured with bromelain treatment. Bromelain is used to treat scleroderma and it is useful against cellulite as it breaks down the deformed collagen tissue surrounding the fat cells and prevents the storage of fat.[48] The antioxidant properties of bromelain have been seen in combating oxidative stress. In a study, the potential of bromelain in the treatment of acne was evaluated due to its various antimicrobial properties; bromelain inhibited the growth of *Staphylococcus epidermidis*, *P. acne*, *S. aureus*, *Corynebacterium diphtheria*, and *E. coli*. Bromelain can be further explored to study it as a bactericidal gel with direct treatment for acne; however, its interaction with other skin proteases and antimicrobial peptides, such as psoriasin, can also be explored. It has also been shown that when bromelain is used with papain, it is good for wrinkles and dry skin. In a dermatological study, by an *in vitro* study it was determined that it had an antifungal effect against *Candida albicans*. Topical preparations of bromelain reduce swelling of insect stings and bites.[49]

Use of Bromelain in Dentistry: Antiplaque substances in toothpaste and other preparations that we use in oral hygiene help preventing tooth decays. Five percent bromelain in toothpaste has been found to be beneficial as an antiplaque agent. It has been reported that the vitamins in

pineapple juice, and especially vitamin C, play an important role in oral hygiene and reduce the risk of gingivitis and periodontal diseases. Furthermore, bromelain increases the body's resistance to bacteria and toxins, improves damaged oral soft tissues, and helps the lymph system to function healthily.[50]

Treatment of Sinusitis: It has been shown that bromelain can help as a supportive treatment to reduce the symptoms of sinusitis. In one study, it was demonstrated that bromelain, when used combined with antibiotics, could reduce the duration of sinusitis symptoms in children, to improve breathing and reduce nasal inflammation. Bromelain provides this by decreasing proinflammatory prostaglandin production and reducing swelling in nasal routes. Bromelain significantly reduces mucus production and improves drainage.[51]

Cosmetic Use of Bromelain: Pineapple has a moisturizing effect as it contains carbohydrates and α-hydroxy acids. It has been reported that pineapple extract can be included in the formulas of cosmetic products created for peeling activity. On the other hand, pineapple extract is used for antiaging and epithelializing. Since pineapple extract has a moisturizing and softening effect on the skin, it is recommended to use it in the formulation of cosmetic products. For that reason, many companies have begun to include bromelain in various skin care products, such as scrubs, masks, moisturizers, bath oils, and acne treatments.[52]

Use in Peyronie's Disease: Peyronie's Disease (PD) is a superficial fibrosing disorder of the penis resulting in plaque formation and penile deformity. They leave permanent scars. These scars and wounds disrupt the organ structure. Since the penis has lost its elasticity, it bends to one side during erection by causing pain. There is no known cure. Though there are some different types of surgery available like plaque incision and excision, grafting, and placement of inflatable penile prosthesis (IPP), none of the surgical options have proven to be effective. Bromelain is known as an effective protein digesting enzyme in stimulating collagenase and breaking down collagen by dissolving the peptide bonds that hold the proteins together.[53,54]

Enhancing Digestion: Some people take bromelain to relieve stomach upset and symptoms of digestive disorders. Bromelain has been successfully used as a digestive enzyme following pancreatectomy, in case of exocrine pancreatic insufficiency. Because of its anti-inflammatory properties, it is used as an adjunct therapy to treat inflammatory bowel disorders. Bromelain has also been reported to heal gastric ulcers in experimental animals and it is stated that bromelain in pineapple juice helps to break down the proteins in the foods taken, to destroy harmful bacteria in the stomach and intestines.[55,56]

Antibiotic Effect: Bromelain can increase tissue permeability and absorption of antibiotics after oral, subcutaneous, or intramuscular administration. Bromelain may increase the amount of antibiotics absorbed by the body. Human urine and blood antibiotic levels were found to be higher with bromelain intaking. In one clinical study, the combination of bromelain and amoxicillin raised the levels of amoxicillin in the blood. Also, some studies suggest that bromelain may increase the body's absorption of tetracycline. In the combined use of bromelain with antibiotics, it was found to be more effective than the antibiotics using alone in the treatment of Staphylococcus infections, thrombophlebitis, urinary tract infections, pyelonephritis, perirectal and rectal abscesses.[55,56]

Use of Bromelain in Sports Medicine: In a study of proteases, including bromelain, it has been reported to shorten the duration of muscle soreness after training compared to placebo. The combination of bromelain and ibuprofen was compared with placebo only. Bromelain has been noted to reduce elbow flexor involvement and pain in weightlifting exercises.[57,58]

Anthelmintic Activities: Leaves of *Ananas comosus* have been traditionally applied as oral anthelminthic medicine in many parts of the world, especially in India. Anthelminthic activity of the leaf extract was investigated. *In vitro* evidence showed that bromelain was used as anthelmintic activities against the gastrointestinal nematodes *Trichuris muris* and *Heligmosomoides polygyrus*.[59]

Pineapple juice is recommended by dietitians for those who want to lose weight as it helps the metabolism of fats and cholesterol.

Side Effects and Toxicity

The pineapple plant does not contain any known toxins. However, when eaten raw and in large quantities, pineapple could produce a burning sensation in the lips and mouth as well as angular stomatitis. Angular stomatitis is an inflammation of the mucous membranes of the mouth, cheeks, gums, lips, tongue, and mouth. The toxicity rate of bromelain is efficiently low when stated as LD50 (lethal dose); in mice, rabbits, and guinea pigs, it is at the level of 10 g/kg. In dogs, the LD50 dose was increased up to 750 mg/kg and no toxicity was observed for six months. No carcinogenicity and teratogenicity were observed in rats given a daily dose of 1500 mg/kg.[60]

The most observed and reported side effect of bromelain is gastrointestinal effects. It is stated that these side effects are caused especially by overdose use. Side effects are generally observed as nausea, vomiting, indigestion and bloating, diarrhea, palpitations, loss of appetite, headache, muscle pain, dizziness, and drowsiness. The use of bromelain is not recommended for people with ulcerative complaints. Due to its effect on blood clotting, bromelain may increase bleeding tendency. Therefore, it is recommended not to take bromelain two weeks before surgery. Some people have allergic reactions to bromelain, such as breathing problems, sore throat, hives, and itchy skin. Allergic reactions to bromelain are more common in those allergic to latex, wheat, celery, papain, carrots, fennel, and pollen. It is necessary to avoid the use of bromelain for those with liver and kidney disease and high blood pressure.[61,62]

Supplements and Dosage

Bromelain is typically taken as a pill or tablet, but you can also find it as a cream for topical use. Bromelain intake is usually not recommended for more than 10 days.

The larger bromelain doses available in supplements are required for maximum health benefits. The researchers at University of Maryland in the U.S. note that standard doses should range from 500 to 1,000 mg three times a day. Specific to certain conditions, it is recommended to take 500 mg per day in divided doses for digestive problems, and 500 mg four times a day for injuries, respectively. It is also recommended taking 500–2,000 mg per day in two divided doses to treat arthritis. However, according to the German Commission E, it is appropriate to take 80–320 mg of bromelain two or three times a day.[63,64]

Drug Interactions

Bromelain can increase the absorption of some antibiotics, especially tetracycline and amoxicillin. Bromelain may interact with sedative medications such as tricyclic antidepressants, barbiturates, and benzodiazepines. Bromelain has been reported to interact with some chemotherapy drugs, such as cisplatin, vincristine, and 5-fluorouracil.[65]

Therapeutic Applications Against Coronavirus: Pneumonia cases with unknown ethology from Wuhan, China, started in December 2019, grew as an epidemic in a very short time, and the number of cases spread all over the world and reached millions. This new virus is highly contagious, and or therefore, the WHO declared the epidemic as a pandemic on March 11, 2020.[66,67]

Though the attempted control of the pandemic has been focused on the development of novel vaccines, the virus has reached the higher level through multiple mutations. When the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) sequences isolated from Coronavirus Disease 2019 (COVID-19) patients were examined, it was determined that the strains from different patients were highly like each other and it was thought that not much variation had yet emerged in the pandemic.[68,69]

COVID-19 is transmitted mainly through droplets, human-human close contact, and aerosols via self-inoculation (transferring the disease from part of the body to another) of the mucus membrane of the eyes, nose, and mouth.[70,71] The most common symptoms at the onset of COVID-19 disease are fever, cough, shortness of breath, and fatigue, whereas other symptoms are noted as sputum, headache, hemoptysis, diarrhea, and lymphopenia.[72]

Cardiovascular disease, diabetes mellitus, conical lung disease, hypertension, and cancer are associated diseases, and the rate of case-fatality is high in adults with severe respiratory symptoms.[73] Vaccination against the disease is still seen as the best choice. It is thought that rapidly increasing the vaccination rates will provide success in the pandemic. In addition to the vaccine applications in the world, many clinical studies are continued in which new agents and drugs whose effectiveness is being investigated are being tested. Chloroquine and hydroxychloroquine, which are stated to be effective in viral cell culture, are among the agents that have been tried for SARS-CoV-2, but sufficient results have not been obtained regarding the efficacy of the treatment. The nucleotide analog Remdesivir is also one of the compounds approved by the Food and Drug Administration. Remdesivir is also administered in combination with other drugs, such as baricitinib.[74] It has been reported that the use of azithromycin in cases of COVID-19 also contributes to the treatment. On the other hand, the RNA polymerase inhibitor favipiravir, which is used in the treatment of influenza, has been approved in many countries and accepted in the treatment protocols of Turkey.[75]

Could Bromelain Be an Alternative Agent in the Treatment of COVID-19?

Antivirals, antimicrobials, anti-inflammatory drugs, some herbal mixtures, and extracts have been put into trials to prevent the progression of the COVID-19. All these remedies showed limited success in curing the disease. However, bromelain inhibits proinflammatory cytokines, primarily IL-6 and TNF-α, which is also considered a hallmark of cytokine storm, especially in patients with COVID-19. It can slow

down the advent of inflammation and prevents escalation with the progression of the disease. On the other hand, previously mentioned physiological effects of bromelain make it one of the potential candidate drugs for the treatment of symptoms of COVID-19 infection. This has been associated with reducing the impact of COVID-19 infection, which causes multi-organ destruction.[76,77]

Bromelain prevents thrombosis by increasing the concentration of plasmin in the blood as well as inhibiting platelet aggregation. Thrombosis and coagulation reduce erythrocyte transport and affect ventilation-perfusion rate in acute respiratory distress syndrome developing in COVID-19 patients.[78] Oxidative stress is a major influence in COVID-19 infection. However, bromelain has proven antioxidant activity, and in this sense, it can reduce cellular oxidative stress, and with this mechanism of action, it can alleviate degenerative tissue damage in the treatment of COVID-19. [39] For the treatment of COVID-19, it is considered to use protease inhibitors that they will prevent the virus from entering the cell. On the other hand, bromelain inhibited SARS-CoV-2 infection in VeroE6 cells by altering ACE-2, TMPRSS2, and SARS-CoV-2 S-protein expression. The cysteine proteolytic activity of bromelain was found to be higher in ACE-2 than in TMPRSS2. A study has indicated that bromelain can inhibit SARS-CoV-2 infection by targeting three hosts ACE-2, TMPRSS2, and SARS-CoV-2 S-proteins. Since bromelain inhibits SARS-CoV-2 infection, and its profound fibrinolytic activity 6 suggests that bromelain or bromelain-rich pineapple could be used as an antiviral against SARS-CoV-2 and future outbreaks of other coronaviruses. [79]

Conclusion

Bromelain is a proteolytic enzyme derived from the pineapple, *A. comosus* (Bromeliaceae) plant. Skin lotions, antiaging creams, and peeling products containing bromelain in the field of cosmetics are widely sold. The potential therapeutic value of bromelain is due to its biochemical and pharmacological properties. As mentioned in this paper, bromelain is administered for its various effects, such as anti-inflammatory, antithrombotic, and anticoagulatory effects. Bromelain can be utilized to treat patients with inflammation and pain and that the compound is well absorbed and with prolonged biological activity. Bromelain is used to protect and treat cancer, immune and cardiovascular diseases. Many clinical studies of bromelain in cancer are clinical trials of bromelain showing its effectiveness for treating various inflammation-based conditions. Studies in recent years have also shown that bromelain has the capacity to change the factors that cause malignation. With the emergence of the COVID-19 pandemic, it is stated that bromelain, which does not show any serious side effects, is open to research in the treatment of COVID-19. All these advantages can be exploited when treating patients with COVID-19. But future approaches will require for more clinical studies in patients with cancer and COVID-19. This substance may be used as alone or in combination with other medications, whether in the topical or oral administration. Finally, bromelain could be a promising candidate for the development of future enzyme therapies in most of the diseases.

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