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Ethnopharmacological Applications of Bromelain in Dentistry and Medicine

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KEYWORDS

Applications, Bromelain,Anti microbial activity, Antifungal, Medicine, Dentistry,

ABSTRACT:

Aim: Bromelain is a protease enzyme generated from various parts of pineapple plant. It is an amalgamation of several thiolendopeptidases, as well as phosphatases, glucosidase, and other enzymes with important pharmacological properties. The development of advanced pharmacologically active substance with minimal side effect remains the gold standard of any new drug development. This review aims to highlight the importance of the enzyme bromelain in modern drug formulations in the field of dentistry.

Material and methods: In vitro and in vivo studies on Bromelain enzyme and its application in dentistry searches were performed in PubMed and Scopus library databases since 2000 till July 2023.

Results:16 studies with full text article were included in this review. The result shows limited research with the potentiality of Bromelain enzyme in the field of dentistry.

Conclusion:In vitro and in vivo research shows that bromelain has a variety of effects namely anti-oedematous, regenerative, and anti-inflammatory propertiesamongmany others the most anticipated being its antimicrobial property which has garnered much interest due to the incessantly increasing antibiotic resistance worldwide. Bromelain has demonstrated a tremendous amount of potential, but additional clinical research is necessary to generate enough evidence-based literature for use in oral healthcare in the future.

INTRODUCTION

The fundamentals of modern pharmacology include foraging for novel physiologically active substances with minimal side effects. Due to the prevalent toxicity of pharmaceutical agents and the increasing spread of antibiotic resistance, the significant development of selective compounds remainsa Hercules task(1)(2).

Generations of indigenous practitioners throughout the world have used herbs and medicinal plants which are currently the focus of extensive research due to their limitless potential for new medication discovery and their unparalleled accessibility to chemical diversity, high therapeutic availability, and relative simplicity of acquisition (2)(3). Compounds found in medicinal plants, either as a whole or in individual portions, can be used therapeutically to create beneficial pharmacological medicines. These plants have grown to be exponentially important as resources of the therapeutic compounds used in contemporary medicines(3).

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One such fruit-based plant which belongs to the Bromeliaceous family, *Ananas comosus*, contains primary sulfhydryl proteolytic enzyme, bromelain, a potential plant-derived substance used in many fields of medicine(2)(4). Fruit Bromelain (EC 3.4.22.33) and stem Bromelain (EC 3.4.22.32) derive from the fruits and stems respectively. It also contains calcium that is organically bound, phosphatases, peroxidases, glucosidase, cellulases, glycoproteins, and a number of protease inhibitors. It also contains different thiol endopeptidases. The enzyme from the stem also contains a small amount of cysteine endopeptidases (ananain, comosain). (Figure :1) (Figure :2)

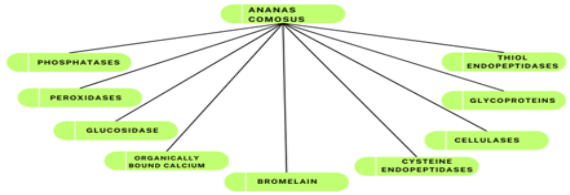

Figure 1: Components of *Ananas comosus*

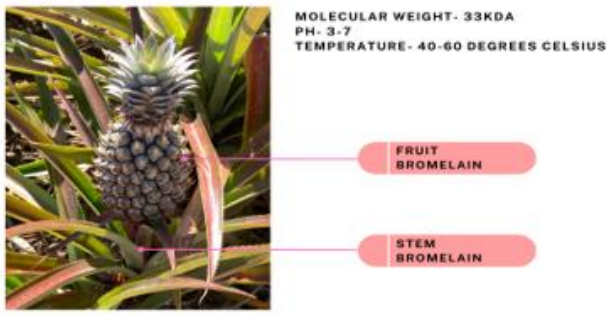

Figure 2: Bromelain its sources and properties.

It has a molecular weight of 33 kDa and consists of 212 amino acids. Hg++, Ag+, Cu++, antitrypsin, estatin A and B, and iodoacetates all impede bromelain. It has a large range of specificity for protein fragmentation and is stable between pH 3 and 7 and temperatures between 40°C and 60 °C. The use of bromelain is widespread not only in the food, pharmaceutical, medical, and cosmetic industries but also in other industries including enzyme-assisted bioprocessing of leather(5).The enzyme is known to have anti-inflammatory, cardio-protective, immune-modulatory, antioxidant, and anti-cancer activities. Besides being used in medicine, bromelain also has numerous other uses in the food business, including in the brewing, meat-processing, textile, and cosmetics sectors. Considering many possible uses for bromelain, both the pharmaceuticals and food sectors' interest in this substance has significantly increased (2).

Material and methods: In order to conduct this review, the following electronic databases: PubMed and Scopus were used to find published articles on bromelain a protease enzyme since 2000 till April 2023. Only studies written in English were included. The databases were searched using keywords and medical subject headings (MeSH) terms in titles as follows: (“Bromelain” AND “uses,” “Bromelain” AND “antimicrobial activity,” “Bromelain” AND “application in dentistry,”. The relevance of the articles was estimated by analysing their title and abstract. The articles meeting all search criteria were evaluated and included in this review.

RESULTS

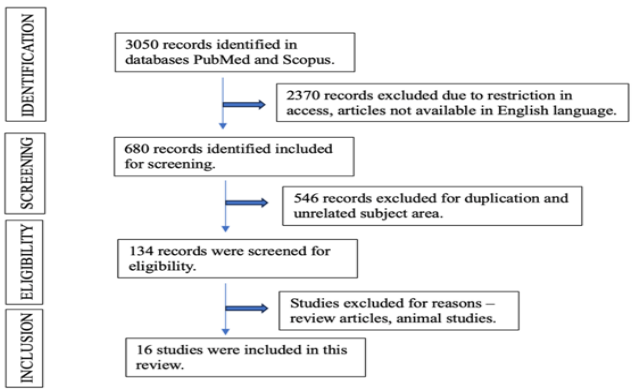

Figure 3: Flow diagram of identification, screening, assessment of eligibility and inclusion of studies in this review

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After the search using appropriate keywords and MeSH terms a total of 3050 articles were identified. These articles were further screened and assessed for eligibility and finally 16 full text articles were included in this review paper.

APPLICATIONS OF BROMELAIN IN MEDICINE AND DENTISTRY(Figure :3)

ANTIBACTERIAL PROPERTY:

Pineapple extract significantly inhibits the growth of both gram-positive and gram-negative bacteria, including *S. aureus*, *S. pneumonia*, *E. coli*, and *P. aeruginosa*(1).Antimicrobial tests suggest activity against organisms causing acne infection among which *S. aureus* was found to be most sensitive to the effects of both raw and refined bromelain extracts, followed by *P. acne*. Peel crude as well as purified extract showed the strongest inhibition of *S. aureus* proving to be a possible protease that may be utilized to treat acne clinically (6). Studies have found significant antibacterial activity against *Enterococcus faecalis* suggesting for use as an endodontic irrigant alternative to NaOCl(7). Due to its synergistic effect with antibiotics showing increased effectiveness in many disease states, it has been found to have wide applications.It also showed efficient activity against oral bacteria leading to growth inhibition and death (2).Ataide *et al* (2017) suggested a novel strategy for using bromelain as an antibacterial agent. The bromelain-loaded bacterial nanocellulose was employed and it was found that Bromelain has considerable antibacterial action when tested against *E. coli*, *S. aureus*, and *P. aureoginosa*. Integration into bacterial nano cellulose further strengthens the antibacterial effect (8). Bromelain can reduce multiplication at concentrations as low as 25% over a 72-hour incubation time and as low as 12.5% over 24 and 48-hour incubations when used against *E. faecalis*, the pathogen that causes root canal infection.(9)

To investigate bromelain's antibacterial effectiveness against isolated strains of *S. mutans*, *E. fecalis*, *Aa*, and *Pg* qualitative *in-vitro* analysis was carried out. In light of the findings of the current investigation, it can be speculated that bromelain may work as an antibacterial agent by preventing bacterial adhesion (10).

The antibacterial activity using the disc diffusion method of the extract of fruit pineapple core (*A. comosus L.Merr.*),was evaluated against the bacteria *S. mutans* and *P. gingivalis*, which are responsible for dental caries and periodontal disease (11). In addition to having phytotherapeutic properties, BROM also has catalytic abilities. According to the study, medication molecules are released by the enzyme that is chemically connected to flake Graphene Oxide and an antibiotic molecule, inhibiting the growth of bacteria that are sensitive to the antibiotic. In contrast to pastes, where the amount of medicine supplied is typically used in excess, the enzyme concentration picked determines how quickly the drug is released (12).

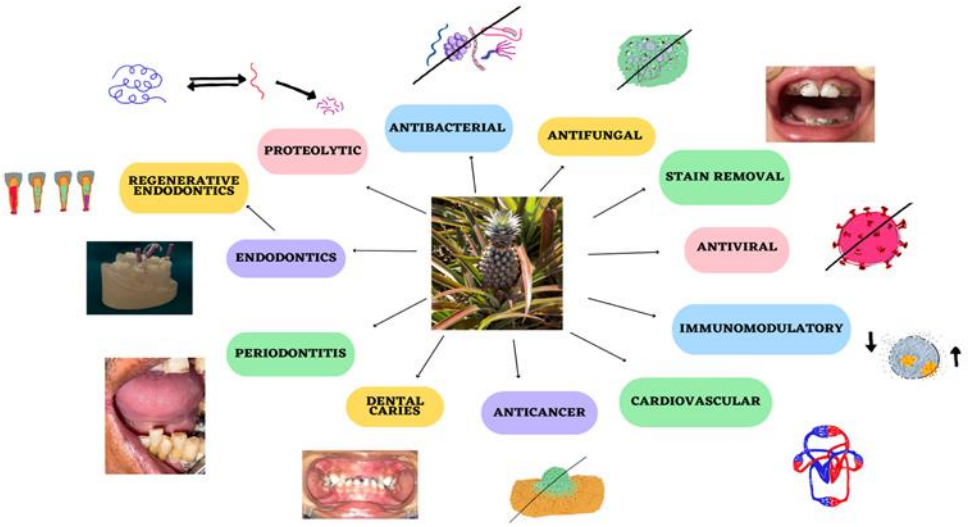

Figure 4: Applications of Bromelain in Medicine and Dentistry

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ANTIFUNGAL PROPERTY

The antifungal qualities of bromelain are different as compared to its demonstration of its microbial activity.According to Lopez-Garcia *et al* in2012(13) , bromelain has powerful antifungal properties that are effective against the economically significant fungal infections like *F.verticillioides*, *F.oxysporum*, and *F.proliferatum*. Bromelain combined with trypsin was shown by Brakebusch*et al*(14) to be fungicidal against *C.albicans*. Bromelain and trypsin have been demonstrated to greatly speed up the phagocytosis and respiratory burst death of *C.albicans*(2). It is possible, though not established, that bromelain takes part in the host's defense mechanism against phytopathogens (15).

ANTIVIRAL

Bromelain may inhibit SARS-CoV-2 infection by attacking ACE2, TMPRSS2, and the SARS-CoV-2 S-protein. (2)According to Akhter *et al (*2021), when taken alone (50 and 100 g/mL) or in combination with acetylcysteine (50 and 100 g/20 mg/mL), bromelain can harm the spike and envelope proteins of the SARS-CoV-2 virus. By preventing SARS-CoV-2 viral binding in VeroE6 cells, bromelain pre-treatment significantly reduced SARS-CoV-2 viral infection and viral RNA transcripts within the cells(16).

IMMUNOMODULATORY PROPERTY

According to a large number of studies, bromelain possesses extremely complex immunomodulatory capabilities that are manifested at several levels of molecular pathways of signalling and modulation of gene expression related to the immune response. For the immune system to function properly and to maintain homeostasis, bromelain has a dual impact on modulating the immune response. Bromelain may produce both a rise and decline in the activity/expression of identical molecules implicated in the immune response, according to the microenvironment of the cell, the presence of inflammation-inducing factors, and, ultimately, the general state of health.(2)

By regulating the synthesis of pro-inflammatory prostaglandins (reducing levels of prostaglandin E2 (PGE2) and thromboxane A2 (TXA-2)), increasing the anti-inflammatory mediators as well as the levels of prostaglandin, decreasing plasma fibrinogen and bradykinin levels (which results in reduced vascular permeability)thereby reducing oedema and pain, bromelain can be used as an alternative to other anti-inflammatory medications.(17)The most notable benefit throughout the surgical convalescence period of chronic rhinosinusitis is the anti-oedema action of bromelain. By reducing oxidative stress and the expression of inflammatory mediators such as Thromboxane A2, Bradykinin, and PGE2, bromelain helps to reduce inflammation in the most prevalent musculoskeletal degenerative illness, osteoarthritis.

Surgery to remove impacted third molars might result in both hard and soft tissue trauma, which could lead to aftereffects like discomfort, oedema, and trismus (18).When taken alone, bromelain had a significant anti-inflammatory effect, but it had no discernible effect when compared to no medication administration. (19)IL-1, IL-6, and IL-8 mRNA levels increased by LPS were reduced by bromelain.(20)

In a clinical trial, Odresi*et al* 2014. (21)established that bromelain had an anti-oedematous effect during third molar surgery. The bromelain-treated group displayed a decreased inflammatory response.The observed outcomes unequivocally showed that bromelain is useful in alleviating postoperative oedema following third molar surgery.(22)Patients undergoing oral surgical procedure may benefit from the use of bromelain as an oral enzyme treatment, particularly following the extraction of impacted third molars.(23)

Various findings demonstrated that bromelain has the ability to reduce postoperative trismus. Numerous studies (Majid & Al-Mashhadani, 2014; Barrera-Nez et al., 2014) have found no evidence to support this conclusion. According to Ghensi*et al*. (2017), distinct etiologies for trismus as opposed to oedema are thought to justify various outcomes. The constraints identified in their research and variables in pain, could be related to the variable in etiology. With a similar impact on the postoperative sequelae as preventative diclofenac sodium, oral bromelain has shown to be an efficient medication to improve Quality of life following surgical extraction of impacted lower third molars (24).Due to its proteolytic, anti-edema anti-inflammatory and antibacterial properties of bromelain, numerous experimental results and clinical trials have shown improved burn and wound healing. (17)

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CARDIOVASCULAR

Studies indicate that bromelain at appropriate doses and time may reduce or minimize symptoms associated with several cardiovascular diseases. It has been demonstrated to inhibit platelet activity in a dose-dependent way and is used to prevent and treat thrombophlebitis because of its anticoagulant and fibrinolytic effects. Acting on the blood clotting system's internal and external pathways and by reducing the production of new fibrin and enhancing serum fibrinolytic activity, it controls the homeostasis of blood coagulation. Low doses had a procoagulant impact, but high amounts had an anticoagulant effect. Based on numerous research bromelain can selectively influence blood coagulation by modifying the level of PGE2 and thromboxane A2. PGE2 and thromboxane A2 activity showed a statistically significant reduction by bromelain, and the ratio of thromboxane A2/prostacyclin (PGI2) was altered in favour of the anti-inflammatory PGI2.(2)

ANTICANCER

Its molecular anticancer activity' precise mechanism is still an enigma. It has been proposed that bromelain's proteolytic and immunomodulatory capabilities may be accountable for of its capacity to reduce tumour cell growth, metastasis, and death. One of bromelain's key properties that effectively inhibits the growth and multiplication of cancer is unquestionably its capacity to cause apoptosis.Multiple investigations using a human prostatic, breast cancer model, stomach, and peritoneal mesothelioma cells have proven the synergistic interaction between cisplatin and bromelain. According to the scientists, bromelain can activate neutrophils to create ROS, which is likely one of the mechanisms behind its anticancer effect.(2)

Additionally, nothing is known about the molecular mechanisms behind bromelain's anticancer action. However, some studies contend that the protease components as well as proteolysis of bromelain play a major role in its anticancer activity. One of the bromelain's identified anti-tumor methods is inducing the differentiation of leukemic cells, which results in the apoptosis of tumor cells. In mouse skin, the apoptosis-inducing genes p53 and Bax are expressed more, which slows the proliferation of cancer cells. The expression of cell survival controllers like Akt and Erk is also reduced, which encourages tumor cell death by apoptosis. In mouse papillomas and cancer models, bromelain also reduces the expression of factors that promote the spread of cancer, such as nuclear factor kappa B (NF-B) and Cox-2.(17)

CARIES

Dental caries, which is the second-leading reason for tooth loss after periodontitis, is one of the most prevalent chronic paediatric disease globally.(25)Chemo mechanical caries removal uses a chemical substance to remove diseased dentin in a minimally invasive manner. Chemo mechanical substances work by removing the outermost layer (the diseased layer), where collagen is broken down, leaving the afflicted dentin, which is demineralized yet capable of becoming remineralized and restored. While the time required to remove carious dentin was practically identical in both the bromelain and papain groups, the amount of residual demineralized dentin was discovered to be lesser in the bromelain group compared to the papain group. One could draw the conclusion that bromelain was superior to papain at removing dental cavities.In compliance with the above properties Tucker *et al* 1995 demonstrated thatbromelain is more efficient than papain at eliminating the remaining carious dentin. This might be because bromelain has a considerably stronger action and is good at breaking down myofibrillar proteins, but papain is not very powerful against collagen. (15)(26)A study was done to examine three minimally invasive caries removal methods, including ART caries removal, chemo mechanical caries removal utilizing bromelain gel, and smart burs. The stereomicroscopic examination demonstrated the superiority of bromelain gels and smart bursts over ART. Additionally, it was discovered that the microhardness levels of bromelain gel were similar to those of healthy dentin. When juxtaposed to other methods, bromelain gel was very effective at removing cavities and reducing microhardness. In paediatric, Minimal Invasive Dentistry plays a significant role. It is regarded as a blessing for children who are uncooperative since it greatly reduces their apprehension or fear of receiving dental care. Because MID avoids the loud noise, vibration, and spray of water of conventional rotational devices, these kids are more afraid of them. Therefore,

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bromelain can be viewed as a successful chemo mechanical caries elimination agent.(25)

PERIODONTITIS

Additionally, it is believed that bromelain prevents periodontitis from developing and worsening by removing crucial cell surface molecules (CD25) from leucocytes (due to its proteolytic activity), reducing an upsurge of periodontal microorganisms (due to its anti-adhesion property), preventing neutrophils from migrating to periodontal sites (because their overactivity damages the periodontium), and down regulating mediators of inflammation (COX-2,TNF)reduced alveolar bone loss and a decrease in the osteoclast genesis process. (17)

REGENERATIVE ENDODONTICS

Biomaterials used in vital pulp therapy must have certain properties, including biocompatibility, anti-inflammatory actions, and the capacity to mineralize and produce new reparative dentin. In this study's inflammation model, bromelain has the capacity to produce calcium nodules. To tackle the challenges associated with the therapeutic management of developing human permanent teeth with necrotic pulps, regenerative endodontics have been proposed. A key element of regenerative endodontic treatment success is the root canal system's decontamination. Because of the thin dentinal walls' potential to enhance the risk of root fracture, mechanical instrumentation is contraindicated. The root canal system should be cleaned and the dentin surface exposed using calcium hydroxide paste or triple-antibiotic paste, according to the AAE. Important components of regenerative endodontic treatment include dentinal tubule exposure, anti-inflammation, and decontamination. Bromelain demonstrated anti-inflammatory and mineralization benefits in this investigation. Additionally, deproteinization and the loss of the collagen network on newly formed dentin were impacts of bromelain. In order to expose dentinal tubules during a regenerative endodontic procedure, bromelain is useful. Considering its deproteinizing and anti-inflammatory properties, these findings collectively imply that bromelain might be a suitable therapeutic agent for application in clinical settings in regenerative endodontics (20).

AUTHOR & YEAR	TYPE OF STUDY	AIM & OBJECTIVES	METHODOLOGY	RESULTS
Inchingolo, F. *et al* 2010(22)	Randomized controlled clinical trial	Evaluated the effectiveness of bromelain in reducing oedema and discomfort associated with upper 3rd molar exodontia.	Efficiency assessment measuring the linear values of the trago-pogonion distances and Visual Analogue Scale (VAS) were used to measure algogens.	The outcomes obtained unequivocally proved that bromelain works well for treating postoperative oedema following 3rd molar surgery.
Chakravarthy, P. K. *et al.* 2012(30)	Randomized clinical study	Compared the stain-removal effectiveness of Glodent to a control dentifrice.	Anterior teeth were photographed, and Adobe Photoshop was used to calculate the brightness or luminosity values.	The test group post-treatment luminance and average stain removal was substantially greater than that of the control group
Praveen NC *et al* 2014(10)	*In- vitro*	Evaluated bromelain's antibacterial effectiveness against periodontal pathogens.	Inbroth technique, the minimum inhibitory concentration of bromelain was examined against *Streptococcus mutans, Enterococcus fecalis, Aggregatibacter actinomycetemcomitans,* and *Porphyromonas gingivalis.*	S. mutans exhibited sensitivity at the lowest dosage of 2 mg/ml, while *P.gingivalis* showed sensitivity at the lowest value of 4.15 mg/ml.

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Ordesi *et al* 2014(21)	Randomized controlled clinical study	Assessed the effectiveness of bromelain's reduction inpost-operative pain and oedema.	After impacted 3rd molar surgery. Group 1 was administered Bromelain and analgesic to Group 2, if required. Pain, oedema, and erythema were assessedin 3 hours, 48 hours, and 7 days were evaluated.	The study group had less postoperative discomfort, oedema, and erythema compared to control group. Analgesic was marginally lower.
Majid *et al* 2014(24)	Randomized, double-blind, placebo-controlled study	Compared the effects of oral bromelain vs oral diclofenac sodium on pain, oedema, trismus, and quality of life (QOL) after surgical removal of impacted lower 3rdmolars.	Patients with impacted mandibular 3rd molar were extracted. The patients were randomly assigned to 3 groups: bromelain, diclofenac, or placebo. Pain, swelling, and trismus were evaluated at 1, 3, and 7 days postoperatively and QOL was assessed as outcome factors.	Bromelain and diclofenac groups demonstrated a substantial decrease in pain when compared to the placebo group. Both treatment groups had a nonsignificant decrease in trismus when compared to the placebo group and had a significant effect on QOL.
Ajibade *et al* 2015(1)	*In- vitro*	Evaluated antibacterial activity of the crude extract of oven dried pawpaw and pineapple on selected bacteria.	Bioactive Compounds were extracted. Antibiotics Susceptibility tests against*Streptococcus pneumomoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli*on the Crude Extracts of *C. papaya* and *A. comosus* in different concentrations.	*A. comosus*showed high zone of inhibition 12.00mm at a concentration of 1.0g /ml.The highest zone of inhibition (13.50mm) was evident against E. coli at a concentration of 1.00g/ml. the test organisms showed multidrug resistance to all the conventional antibiotics at a concentration of 20µg.
Singh, Tejpal *et al* 2016(23)	Randomized clinical study	Evaluated the effect of bromelain on pain and swelling after surgical removal of 3rd molars.	Surgically removed impacted mandibular 3rdmolars were administered bromelain along with amoxicillin. Post-operative pain evaluation onday 1, 3, and 7 using visual analogue scale.	Out of the total 40 patients, bromelain was effective in 28 (70%) patients. In these patients, there was reduction in swelling and pain after taking bromelain.
Ghensi *et al* 2017(19)	Randomized controlled clinical trial	Evaluated the effect of oral administration of bromelain on discomfort after mandibular third molar surgery.	After single mandibular impacted 3rd molar surgery participants were randomly assigned to receiving no drug (control group, Group A), postoperative 40 mg bromelain every 6 hours for 6 days (Group B), preoperative 4 mg dexamethasone sodium phosphate as a submucosal injection (Group C), and preoperative 4 mg	On postoperative day 2, in both Groups C and D, onday 7, Group D showed a there was a statistically significant reduction in facial oedema with the control group. The combined use of bromelain and dexamethasone (Group D) induced a

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			dexamethasone sodium phosphate as a submucosal injection plus postoperative 40 mg bromelain every 6 hours for 6 days (Group D). Maximum interincisal distance, facial contours and pain were measured at postoperative days 2 and 7. Patient perception of the severity of symptoms was assessed with a follow-up questionnaire (PoSSe scale)	statistically significant reduction in the total number of analgesic tablets taken after surgery compared with the control group. The treatment groups had a limited, nonsignificant effect on trismus when compared with the control group.
Liliany *et al* 2018 (9)	*In- vitro*	Analysed the enzymatic activity of bromelain extracted from pineapple hump and investigated the antibacterial effect of bromelain against *E. faecalis.*	Extraction,ammonium sulphate fractionation, dialysis, and ion exchange chromatography were carried out to purify the sample and antibacterial activity of bromelain extract against *E. faecalis* was investigated using a minimum inhibitory concentration (MIC). The inhibition zones were tested using a variety of bromelain extract doses.	Bromelain specific activity in crude extract was 62.89 U/mg,50.99 U/mg using ammonium sulphate fractionation, 54.59 U/mg using dialysis, and 152.38 U/mg with ion exchange chromatography. Bromelain extract inhibited bactericidal activity against *E. faecalis.* The inhibition test utilising a bromelain extract purified by ion exchange chromatography revealed that a dose as low as 12.5% was effective in preventing *E. faecalis* growth.
Amini *et al* 2018(11)	*In- vitro*	The purified bromelain was subsequently tested for antibacterial activity against *S. mutans* and *P. gingivalis*.	Bromelain from pineapple core was refined by multistep fractionation. Proteolytic activity of bromelain was determined using Kunitz method. Protein content of bromelain was determined using Lowry method using BSA as standard solution. Determination of Antibacterial Activityagainst *S. mutans* and *P. gingivalis* using the disc diffusion technique.	Proteolytic activity was demonstrated at specific activity of 52.318 Unit/mg. Fractionation with acetone yielded the specific activity of 87.778 Unit/mg and ammonium sulphate fractionation generated a specific activity value of 260 Unit/mg which after dialysiswas enhanced to 340.926 Unit/mg. The ammonium sulphate fraction had a significant activity against *P. gingivalis*

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				bacteria.
Reddy VK *et al* 2019(15)	*In- vitro*	Evaluated and compared bromelain with papain as the chemo mechanical caries removal agent in relation to their efficacy.	30 extracted primary molars with activedentinal carious lesions were cut into half. Group I cavities were treated using papain gel, whereas Group II cavities were made with bromelain gel. Timetaken was recorded taken to remove caries in both groups. The quantity of demineralized dentin left was quantified using a stereomicroscope and weld check software.	The mean residual carious dentin thickness acquired from group II (bromelain) was 36.74 m, which was significantly lower than the mean obtained from group I (papain) of 73.84 m. The mean time taken in group II (bromelain) was 335.30 seconds, which was substantially identical to group I (papain)352.33 seconds.
Khatib, M.S *et al* 2020 (28)	*In- vitro*	Evaluated and compared the deproteinizing effect of sodium hypochlorite, bromelain, and papain on micro tensile bond strength of composite resin to etched dentin.	Based on the process of dentindeproteinization. Group I: only etching; group II: deproteinized with 5.25% sodium hypochlorite; group III: deproteinized with 8% bromelain enzyme; and group IV: deproteinized with 8% papain enzyme. The sample surfaces were blotted dry, bonded, and rebuilt with light cure bulk fill composite. The teeth were sectioned into 1 mm thick slabsand tested a tensile load at a crosshead speed of 0.5 mm/minute until it cracked.	Higher mean bond strength was recorded in group IV followed by group III, group II, and group I, respectively. Group III presented a statistically significant highest mean score compared to other study groups However, the mean micro tensile bond strength score did not differ significantly between group III and group IV.
Kasraie *et al* 2020(27)	*In- vitro*	Assessed the impact of surface treatment of dentin with 5% bromelain and 5% trypsin on the microleakage of composites.	Class V cavities (n = 40) were etched with 37% phosphoric acid, 5% bromelain and 5% trypsin incontrol group and test groups respectively. In one group, Adper Single BondOptiBond was used in the cavity wall,restored with	No significant difference was observed in the occlusal marginal microleakage of study groups (p = 0.43), but the difference in microleakage of

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			Z250 compositeand marginal microleakage were examined.	cervical margins was significant (p = 0.000).
Abinaya, R. *et al* 2020(25)	*In- vitro*	Compared the caries removal efficacy of 3 minimally invasive techniques and analyzed qualitatively under stereomicroscopy and quantitatively using Vickers hardness test.	30 non-carious anterior primary teeth were demineralized and validated using RadioVisioGraphy. Bromelain gel, smart bur, and atraumatic restorative technique (ART) samples were separated into three groups. Stereomicroscopy was used to determine thecaries removal and microhardness test was performed.	Bromelain gel and smart bursts outperformed ART in stereomicroscopic examination. Bromelain gel was shown to have microhardness values equivalent to healthy dentins with a statistically significant result.
Mavani *et al* 2021(7)	*In- vitro*	Assessed the antimicrobial efficacy of pineapple-orange eco-enzymes (M-EE) and papaya eco-enzyme (P-EE) at different concentrations and fermentation periods against *Enterococcus faecalis*(EF), compared to 2.5% NaOCl.	EF growth observation was used to calculate the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of M-EE and P-EE. M-EE and P-EE demonstrated MIC at 50% concentrations and MBC at 100% concentrations.	When comparing M-EE and P-EE at 50% and 100% to 2.5% NaOCl, there was no significant difference in antibacterial effect. P-EE at 25% and 0.78% concentrations inhibited EF more effectively after 6 months of fermentation than at 3 months. M-EE and P-EE had antibacterial activities equivalent to 2.5% NaOCl at 100% and 50% concentrations.
Hong, J.-H *et al* 2021(20)	*In- vitro*	Investigated the anti-inflammatory effects of bromelain on lipopolysaccharide (LPS)-induced human dental pulp cells (hDPCs).	The WST-1 test was used to assess cell viability following bromelain administration. Anti-inflammatory mechanism was determined using immunofluorescence labelling and Western blots. Alkaline phosphatase and Alizarin red staining were used to confirm the development of mineralization nodules.	Bromelain at 2.5, 5, 10, or 20 g/mL had no effect on the viability of hDPCs. Bromelain substantially reduced the levels of interleukin-1, interleukin-6, interleukin-8, ICAM-1, and VCAM-1 in hDPCs activated by LPS. Bromelain therapy lowered p65 phosphorylation in the cytoplasm and nucleusextracellular signal-related kinases

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				(ERK) and p38 mitogen-activated protein kinases (p38) substantially. Bromelain also increased ALP activity and the production of mineralized nodules.

Table 1: BROMELAIN STUDIES IN DENTISTRY

PROTEOLYTIC ACTIVITY

According to reports, the activity of proteolysis agents may decrease the amount of protein in acid-etched dentin, which may enhance the depth of penetration of resin monomers into the collagen network of demineralized dentin and lead to the formation of more stable hybrid layers at the dentin-composite interface. While the microleakage at the BG's occlusal and cervical edges was reduced, the current investigation indicated.(27)

According to studies, the problem of nano leakage can be resolved by removing damaged collagen with a deproteinizing agent. Because it modifies the dentin's surface's chemical makeup, it resembles scratched enamel, a more reliable and hydrophilic substrate for bonding. In this work, the deproteinizing effects of papain, bromelain and sodium hypochlorite were compared and evaluated in relation to the micro tensile bonding capacity of composite resin to etched dentin. The dentin substrate is changed by the deproteinizing agents papain and bromelain, which strengthens the binding between etched dentin and composite resin. Bond strength appears to be greater after bromelain and papain use than after NaOCl use.(28)

Bromelain has been demonstrated to have an anthelmintic impact against gastrointestinal nematodes in numerous *in vivo* and *in vitro* experiments. The outcomes show that bromelain's antiparasitic activity is due to its proteolytic characteristics. Bromelain has been found to have an anthelmintic impact against gastrointestinal nematodes in numerous *in vitro* and *in vivo* experiments.(2)

STAIN REMOVAL

Several studies have reported the use of clinical indices for stain evaluation. In one of the studies, Bromelain is a cysteine protease (endopeptidases). Which, unlike hydrogen peroxide treatment, showed only very minor interprismatic dissolving, are the only non-cytotoxic agents and have a cysteine in their active site that covalently links to target proteins for subsequent cleavage.(29)All over-the-counter bleaching products had a maximum effect of stain removal; however, hydrogen peroxide might whiten teeth even more. When compared to hydrogen peroxide, bromelain treatment had a less dramatic but still noticeable whitening impact. It was also neither cytotoxic nor did it affect the surface of the enamel.(30)

SIDE EFFECTS

According to research, taking bromelain may cause allergic reactions in certain people. People with pineapple allergies are particularly at risk [30]. Bromelain can result in IgE-mediated respiratory allergies in these persons, which can lead to breathing problems, blocked sinuses, angioedema, wheezing, and coughing.(2)

DISCUSSION

Every year, at least 700,000 individuals perish from illnesses brought on by resistant bacteria each year, according to the WHO and the OECD. With the escalating cases of drug-resistant pathogen there will be rise in cost of hospitalization and increased burden in healthcare establishments, overall increasing economic cost per year which would impair the healthcare system especially for developing and underdeveloped countries.(31)With the need to look for novel alternative treatments as well as new medications, there has been a tremendous surge in study into the possible uses of natural ingredients in dentistry. (7)(17)The properties of high efficiency, low toxicity, wide availability, and relative ease of acquisition has piqued the insatiable curiosity of

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scientists.(2)Several studies have produced positive findings. with the utilization of medicinal peptides and proteins with inherent antibacterial properties, particularly when combined efficacy when used in conjunction with traditional chemotherapeutic agents, reduces antibiotic use, and may reduce examples of chemotherapeutic drug resistance.(17)Commercially purified bromelain is expensive. Development of approaches to decrease the price of bromelain production, as well as modifications to its purification and stabilisation approaches, in conjunction with studies on the beneficial activities of bromelain is the need of the hour. An absolute necessity is the production of these compounds in an environment conscious manner. Interestingly bromelain extraction has been attempted with quite a success from fruit processing industry wastes, which have previously raised environmental problems. Amalgamation of innovative methods with novel bromelain production systems can be anticipated to render bromelain production simple, efficient, and cost-effective, resulting in the creation of stable, ultrapure, and affordable bromelain.(2)

CONCLUSION

This review displays a wide range of potential applications of bromelain showing substantial promise in healthcare. With these inexhaustible opportunities with bromelain, the world's demand of this substance is constantly rising.

In summary, bromelain is a bioactive compound of excellent scientific and commercial interest with very minimal side effects; however, there are various sector that need to be researched in terms of purification, stabilisation, and thorough knowledge of the mechanisms of action, so that bromelain's activities with several actions can be used effectively.

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