Original Article

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Dentistry Section

Assessment of Anti-inflammatory and Antioxidant Properties of Trypsin, Bromelain, Rutoside and Glucosamine Combination Gel: An In-vitro Study

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ABSTRACT

Introduction: Inflammation and oxidative stress play key roles in the pathogenesis of various musculoskeletal and soft tissue disorders. Conventional pharmacologic therapies, such as Non-steroidal Anti-Inflammatory Drugs (NSAIDs), are associated with several adverse effects, prompting interest in safer, biologically active alternatives. Trypsin and bromelain are proteolytic enzymes known for their anti-inflammatory activity, while rutoside exhibits potent antioxidant and vascular protective properties. Glucosamine, commonly used for joint health, contributes to cartilage repair and has shown mild anti-inflammatory effects. The combination of these agents in a topical gel formulation may offer synergistic benefits in managing inflammation and oxidative stress locally.

Aim: The present study examined the anti-inflammatory and antioxidant properties of trypsin, bromelain, rutoside, and glucosamine combination.

Materials and Methods: The present in-vitro study was conducted at Gold lab, Department of Pharmacology, Saveetha Dental College and Hospital, Chennai, Tamil Nadu, India, from January to August 2024. The chemicals involved in the process were sourced from SISCO Research Laboratories private limited. The active pharmacological ingredients like trypsin, bromelain, rutoside and glucosamine were mixed and tested. The anti-inflammatory and antioxidant properties of both the formulations were investigated. Albumin denaturation assay for anti-inflammatory activity and 1,1-Diphenyl-2-Picrylhydrazyl (DPPH) assay for antioxidant activity were performed. Student t-test was performed to determine the significance, where p-value less than 0.05 were considered statistically significant.

Results: The combination gel exhibited a dose-dependent increase in both anti-inflammatory and antioxidant activities. Anti-inflammatory activity, assessed via the albumin denaturation assay, increased from 51.74% at 20 µg/mL to 85.02% at 100 µg/mL, closely approaching the inhibition shown by the standard drug diclofenac sodium (94.53%). Similarly, in the DPPH assay, antioxidant activity rose from 41.26% at 20 µg/mL to 95.98% at 100 µg/mL, surpassing the activity of ascorbic acid (86.86%) at the highest concentration. Statistical analysis confirmed that these increases were highly significant ($p<0.05$).

Conclusion: The in-vitro findings demonstrated that the trypsin, bromelain, rutoside, and glucosamine combination gel possessed strong, concentration-dependent anti-inflammatory and antioxidant properties. These results suggest its potential as a topical therapeutic alternative to conventional NSAIDs for localised treatment of musculoskeletal and inflammatory conditions. Further in-vivo and clinical studies are recommended to validate its safety, efficacy, and therapeutic applicability.

Keywords: Inflammation, Muscle-joint disorders, Oxidant, Pain, Quality of life

INTRODUCTION

Inflammation and oxidative stress are interrelated biological responses that contribute significantly to the pathogenesis of various musculoskeletal, connective tissue, and dermatological disorders [1]. While inflammation serves as a protective mechanism to eliminate harmful stimuli and initiate healing, chronic or dysregulated inflammation can lead to tissue damage, pain, and functional impairment. Likewise, oxidative stress, resulting from an imbalance between free radicals and antioxidant defenses further exacerbates tissue injury and inflammatory cascades [1,2]. NSAIDs are commonly used to manage pain and inflammation. However, prolonged use of NSAIDs is often associated with gastrointestinal, renal, and cardiovascular side-effects, particularly in vulnerable populations. This has led to a growing interest in the development of safer, locally acting alternatives using naturally derived compounds with known biological activity [1,2].

Trypsin is an enzyme that breaks down proteins into smaller peptides. It helps to manage inflammation by breaking down proteins involved in the inflammatory process, aiding tissue repair [3]. Its anti-inflammatory effects make it useful in treating conditions characterised by pain, swelling, and tissue injury [4,5]. Bromelain is a natural enzyme found in pineapples, valued for its ability to reduce inflammation and relieve pain. It works by blocking certain compounds that cause swelling and discomfort. Bromelain also aids in healing and has been used to help with conditions like arthritis, sinus issues, and sports injuries [6]. Rutoside, or rutin, is a natural compound found in certain fruits and plants. It's known for its strong antioxidant and anti-inflammatory benefits, helping to protect cells from damage and reduce swelling. Rutoside also strengthens blood vessels, making it useful for supporting vascular health and relieving conditions like varicose veins and joint discomfort [6,7]. Glucosamine is a natural substance found in cartilage that plays a key role in maintaining joint health. It helps rebuild and maintain cartilage, which can reduce joint pain and stiffness, especially in people with osteoarthritis. By easing inflammation, glucosamine supports better movement and overall joint comfort [8-10].

Combining Trypsin, Bromelain, Rutoside, and Glucosamine into a single gel offers a holistic approach to managing pain and musculoskeletal disorders. Each ingredient brings its own strengths: Trypsin helps reduce inflammation, bromelain eases pain and swelling, rutoside fights oxidative stress, and glucosamine supports cartilage health. Together, they might work better than any

one of these treatments alone [9-11]. The primary objective was to evaluate the anti-inflammatory and antioxidant activity of the Trypsin, Bromelain, Rutoside and Glucosamine combination gel. The outcomes of this study were intended to support the rationale for further preclinical and clinical investigations into the therapeutic utility of this multi-component gel as a complementary or alternative modality for inflammation-related conditions.

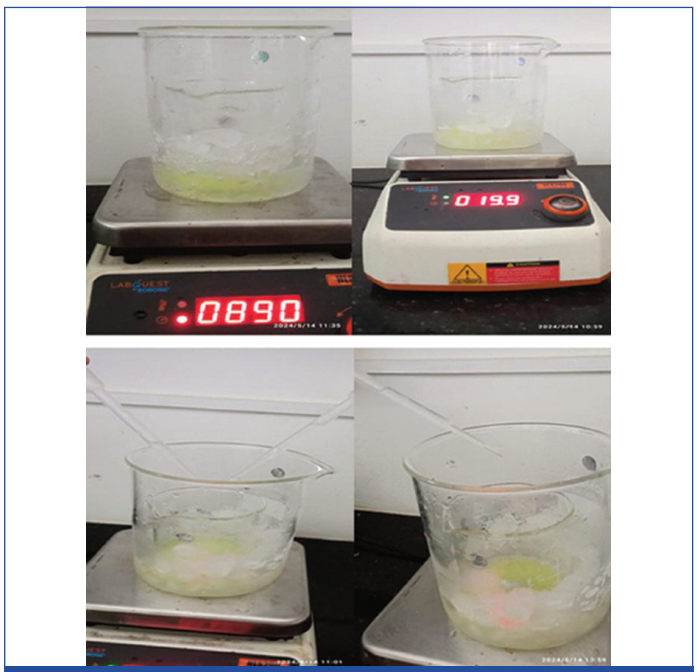
The null hypothesis of the study stated that the combination gel containing Trypsin, Bromelain, Rutoside, and Glucosamine does not exhibit significant anti-inflammatory or antioxidant activity whereas alternate hypothesis states that the combination gel can show significant anti-inflammatory or antioxidant activity.

MATERIALS AND METHODS

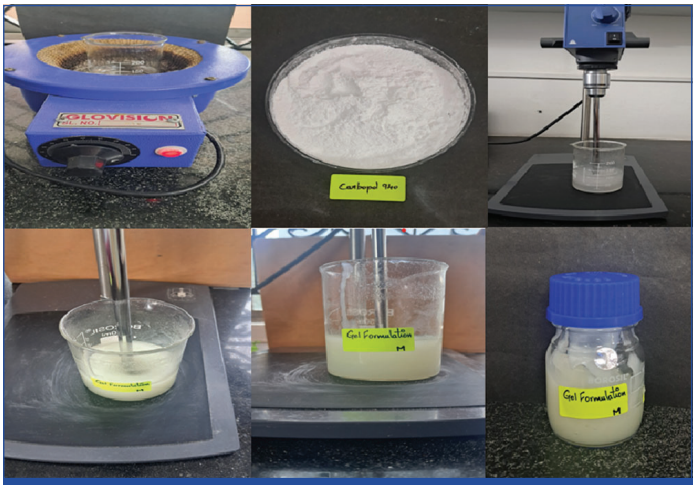
The present in-vitro study was conducted at Gold lab, Department of Pharmacology, Saveetha Dental College and Hospital, Chennai, Tamil Nadu, India, from January to August 2024. The chemicals involved in the process were sourced from SISCO Research Laboratories private limited. The active pharmacological ingredients like trypsin, bromelain, rutoside and glucosamine were mixed and tested. The study was approved by the Institutional Scientific Review Board, with reference number SRB/SDC/OMED-2204/24/460.

Study Procedure

The gel was prepared through a controlled and systematic process involving precise measurement, dissolution, and mixing of components to ensure a homogenous and stable formulation. All active pharmaceutical ingredients, including trypsin (50 mg), rutoside (50 mg), bromelain (50 mg), and glucosamine (50 mg), were accurately weighed using an analytical balance. These were gradually dissolved in a suitable solvent system placed in an ice bath to preserve the integrity of thermolabile compounds. Continuous gentle stirring was performed to aid dissolution and prevent degradation of activities. The required amount of carbopol 940 was weighed and dispersed in purified water, which had been preheated to approximately 50-60°C. A high-shear mixer was used to facilitate proper dispersion and prevent clumping of the Carbopol particles. The dispersion was mixed until the Carbopol was fully hydrated and a uniform, lump-free gel base was formed. Once the base achieved a smooth consistency, the previously prepared active mixture was slowly incorporated into the gel base under continuous stirring [Table/Fig-1,2]. The pH of the gel was adjusted using a neutralising agent such as triethanolamine to activate the gelling property of Carbopol and to ensure compatibility with skin. The final formulation was mixed until a smooth, homogeneous gel was obtained. The prepared formulations were subsequently evaluated for their anti-inflammatory and antioxidant properties using appropriate in-vitro models. The gel was transferred into clean, air-tight containers and stored at room temperature for further evaluation and application [7-10].



[Table/Fig-1]: Shows the mixture was prepared using a method that involved dissolving the components in an ice bath, with precise weighing and mixing procedures.



[Table/Fig-2]: The images depict the formulation of a gel using Carbopol 940 as the gelling agent. The process involves heating the solvent or water, followed by the dispersion of Carbopol. A high-shear mixer is used to ensure uniform mixing and dissolution of the ingredients. The gel is continuously stirred until a smooth, consistent formulation is achieved. The final product is stored in a bottle for further testing or application. This gel formulation likely incorporates active compounds, such as trypsin, rutoside, bromelain, and glucosamine, for potential anti-inflammatory therapeutic use.

Anti-inflammatory activity: The anti-inflammatory activity was assessed using the albumin denaturation method. The biosynthesized glucosamine and bromelain trypsin rutoside combination gel were tested at concentrations ranging from 20-100 µg/mL, combined with 1% Bovine Serum Albumin assay (BSA) at varying concentrations (80, 60, 40, 20, 0 µg/mL) in a microtitre plate. Dimethyl sulfoxide (DMSO) served as the control, while diclofenac sodium was used as the standard drug. The microplates were incubated at room temperature for 15 mins, followed by further incubation at 55°C for 20 minutes. Absorbance readings were taken at 600 nm, and the results were recorded.

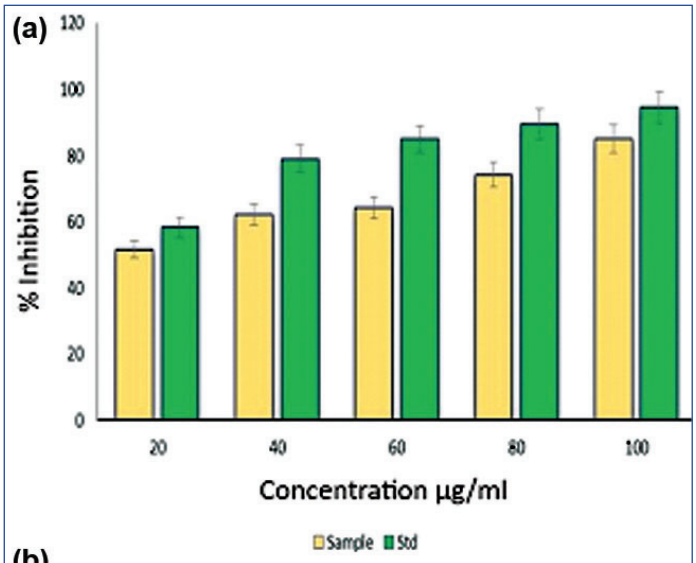
Antioxidant activity: The procedure was carried out following (Abida A et al., 2023) [12] with a slight modification. Using the stable radical DPPH, the ability of Glucosamine and Bromelain-Trypsin-Rutoside combination gel and regular L-ascorbic acid to scavenge free radicals was assessed. 1 mL of Glucosamine and Bromelain-Trypsin-Rutoside combination gel at various concentrations (20-100 µg/mL) was mixed with 1 mL of 2,2-DPPH solution (1 mM in methanol) and vortexed well. Following that, the mixture was provided with a 30-minute incubation period at ambient humidity in the absence of light. Using a Ultraviolet (UV) single bond Vis spectrophotometer, the absorbance was measured at 517 nm methanol was used as a blank solution and DPPH was used as the control (all the reagents were utilized except for the sample). The free radical scavenging activity was given in percentage.

STATISTICAL ANALYSIS

All experiments were performed, and data were expressed as mean±Standard Deviation (SD). The percentage inhibition of anti-inflammatory (albumin denaturation assay) and antioxidant (DPPH assay) activities was calculated for each tested concentration. Data analysis was carried out using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Student t-test was performed to determine the significance, where p-value less than 0.05 were considered statistically significant.

RESULTS

Anti-inflammatory activity: The anti-inflammatory activity of the test formulation containing trypsin, rutoside, bromelain, and glucosamine- was evaluated at concentrations ranging from 20 to 100 µg/mL using the albumin denaturation assay. A dose-dependent increase in percentage inhibition was observed, with activity rising from 51.74% at 20 µg/mL to 85.02% at 100 µg/mL. The standard drug, diclofenac sodium, showed inhibition ranging from 58.35% to 94.53% across the same concentration range. Notably, at the highest tested concentration (100 µg/mL), the test formulation's anti-inflammatory activity (85.02%) closely approached that of the standard (94.53%), indicating strong potential for therapeutic application [Table/Fig-3a,b]. These results suggest a synergistic interaction among the components of the formulation, each of which is known for its individual anti-inflammatory properties [Table/Fig-4]. Data were presented as mean±SD of three independed experiments.



(b)

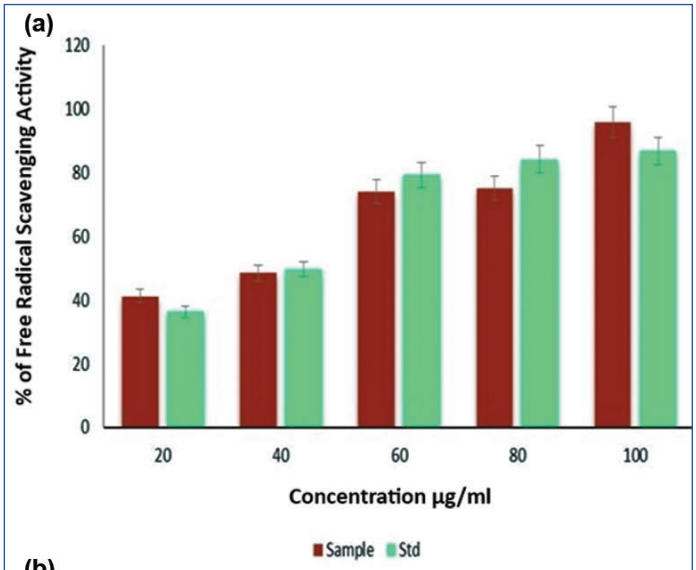
S.no	Concentration	Sample	Standard drug
1	20	51.74±1.2	58.35±1.0
2	40	63.21±1.5	70.12±1.3
3	60	71.89±1.1	79.83±1.2
4	80	79.46±1.4	87.26±1.1
5	100	85.02±1.3	94.53±0.9

[Table/Fig-3a,b]: Comparison of the anti-inflammatory activity (% inhibition) of the test formulation (containing trypsin, rutoside, bromelain, and glucosamine) with a standard anti-inflammatory agent across various concentrations (20-100 µg/ml).

Concentration (µg/mL)	Test formulation (% inhibition±SD)	Standard drug (% inhibition±SD)	Significance (Student t-test)
20	51.74±1.2	58.35±1.0	(0.0209) p < 0.05 (T vs S)
40	63.21±1.5	70.12±1.3	(0.0407) p < 0.05 (T vs S)
60	71.89±1.1	79.83±1.2	(0.0111)p < 0.05 (T vs S)
80	79.46±1.4	87.26±1.1	(0.0201)p < 0.05 (T vs S)
100	85.02±1.3	94.53±0.9	(0.0186) p < 0.05 (T vs S)

[Table/Fig-4]: Pair-wise comparisons within each group, Test applied - Student's t-test, and p<0.05 was considered statistically significant.

Antioxidant activity: The antioxidant potential of the same formulation was assessed using the DPPH radical scavenging assay. As shown in the results, there was a progressive increase in free radical scavenging activity with increasing concentration of the formulation. The test formulation showed 41.26% inhibition at 20 µg/mL, which increased to 95.98% at 100 µg/mL. Interestingly, at the lower concentrations (20 and 40 µg/mL), the test formulation demonstrated higher antioxidant activity than the standard (ascorbic acid), and at the highest concentration, the sample surpassed the standard (95.98% vs. 86.86%). This enhanced activity can be attributed to the synergistic antioxidant effects of the individual components. Rutoside, a known flavonoid, provides direct free radical scavenging activity. Bromelain and trypsin contribute by modulating oxidative inflammatory pathways, while glucosamine aids in mitigating oxidative stress commonly associated with joint degradation [Table/Fig-5a-c].



(b)

S.no	Concentration	Sample	Standard drug
1	20	41.26±1.20	36.31±1.01
2	40	48.49±0.98	49.7±1.05
3	60	73.97±1.02	79.31±1.1
4	80	75.24±1.15	84.2±1.025
5	100	95.98±.07	86.86±0.99

(c)

Concentration (µg/mL)	Test formulation (% inhibition±SD)	Standard drug (% inhibition±SD)	Significance (Student t-test)
20	41.26±1.20	36.31±1.01	(0.0492)p < 0.05 (T vs S)
40	48.49±0.98	49.7±1.05	(0.0461) p < 0.05 (T vs S)
60	73.97±1.02	79.31±1.1	(0.0358)p < 0.05 (T vs S)
80	75.24±1.15	84.2±1.025	(0.0158)p < 0.05 (T vs S)
100	95.98±.07	86.86 ±0.99	(0.0376) p < 0.05 (T vs S)

[Table/Fig-5a-c]: Free radical scavenging activity (% inhibition) of the test formulation (containing trypsin, rutoside, bromelain, and glucosamine) compared with a standard antioxidant agent across concentrations ranging from 20 to 100 µg/mL. Data were presented as mean±SD of three independent experiments.

DISCUSSION

The present in-vitro study demonstrated significant anti-inflammatory and antioxidant properties of a novel gel formulation containing trypsin, bromelain, rutoside, and glucosamine, with both effects showing a clear dose-dependent pattern. These findings support the hypothesis that the synergistic action of the selected biologically active components offered promising therapeutic potential as a topical agent for localised inflammation and oxidative stress [11-13].

Trypsin and bromelain, as proteolytic enzymes, are known to modulate proinflammatory mediators, degrade fibrin clots, and reduce vascular permeability and oedema [14]. Rutoside, a flavonoid, has demonstrated inhibition of inflammatory cytokines

{e.g., Tumour Necrosis Factor (TNF)-α and Interleukin (IL)-1β}, while also stabilising capillary walls [15-17]. Glucosamine, frequently used in the management of osteoarthritis, has been shown to reduce expression of inflammatory markers such as Cyclooxygenase (COX)-2 and nitric oxide synthase in synovial tissues [18].

The present in-vitro study evaluated the anti-inflammatory and antioxidant properties of a novel gel formulation containing trypsin, rutoside, bromelain, and glucosamine. The findings indicated that the formulation demonstrates significant biological activity in a dose-dependent manner, making it a promising candidate for the treatment of inflammation and oxidative stress-related disorders. The percentage inhibition increased with concentration, with the highest activity observed at 100 µg/mL (85.02%), which closely approached the inhibition level of the standard drug diclofenac sodium (94.53%). This suggested that the test formulation exhibits potent anti-inflammatory potential. These results align with prior studies that have reported enhanced anti-inflammatory responses when such agents are used in combination. Previous research has demonstrated that enzyme-flavonoid formulations can achieve comparable outcomes to NSAIDs while avoiding their associated gastrointestinal and renal side effects [19,20]. The statistically significant increase in anti-inflammatory activity with concentration ($p<0.005$) reinforces the potency of this multi-component formulation and indicates its suitability for further preclinical evaluation in models of arthritis, tendinitis, or post-traumatic soft tissue inflammation.

In the DPPH radical scavenging assay, the formulation demonstrated superior antioxidant capacity, with 95.98% inhibition at 100 µg/mL, exceeding the standard ascorbic acid (86.86%). The results show that the formulation not only acts as an effective free radical scavenger but may also provide sustained protection against oxidative stress, which is closely linked to chronic inflammation and degenerative conditions. The potent antioxidant activity observed may be attributed primarily to rutoside, which has a strong radical-quenching effect through hydrogen donation and metal ion chelation [16,17]. Interestingly, glucosamine has also been reported to suppress oxidative damage by improving mitochondrial function and decreasing ROS generation in inflamed tissues [18].

The null hypothesis of the study stated that the combination gel containing Trypsin, Bromelain, Rutoside, and Glucosamine does not exhibit significant anti-inflammatory or antioxidant activity whereas alternate hypothesis stated that the combination gel can show significant anti-inflammatory or antioxidant activity. The results of this study demonstrated that the gel formulation possessed strong anti-inflammatory and antioxidant activities, particularly at higher concentrations thus rejecting null hypothesis and accepting alternate hypothesis. The close performance of the sample to that of standard pharmaceutical agents like diclofenac and ascorbic acid suggests that it may serve as a natural, effective, and safer alternative in managing inflammatory conditions such as arthritis, musculoskeletal injuries, or skin inflammation. Future in-vivo studies and clinical trials are warranted to validate these findings and explore potential formulations for therapeutic use. The results suggest that this combination gel may offer a topical, well-tolerated alternative to systemic NSAIDs, especially in populations sensitive to gastrointestinal or cardiovascular side effects. Topical application allows localized delivery, potentially improving patient compliance and minimising systemic exposure.

Limitation(s)

However, the present study is limited to in-vitro findings. Future studies should explore cytotoxicity and skin penetration. In-vivo animal models of arthritis or inflammation followed by clinical trials to assess safety, efficacy, and patient outcomes. Furthermore, exploring formulation stability, shelf-life, and release kinetics of active compounds could help in optimising the commercial viability of the product.

CONCLUSION(S)

The results of the present in-vitro study indicate that the combination gel containing trypsin, bromelain, rutoside, and glucosamine exhibits significant, dose-dependent anti-inflammatory and antioxidant activities. The formulation effectively inhibited protein denaturation and demonstrated strong free radical scavenging capacity, comparable to standard pharmacological agents such as diclofenac sodium and ascorbic acid. These findings support the therapeutic potential of this multi-component gel as a topical alternative for managing localised inflammation and oxidative stress, particularly in musculoskeletal and joint-related disorders. However, as the current data are limited to in-vitro assays, further in-vivo studies and clinical trials are essential to confirm efficacy, assess safety, and evaluate pharmacokinetics and long-term stability. This formulation may represent a promising step toward developing safer, plant and enzyme-based interventions for inflammatory conditions, especially in populations where NSAID use is contraindicated or poorly tolerated.

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