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Original Article

Hepato(Geno)toxicity Assessment of Different Bromelain Food Supplements in HepG2 Cell Line Model by the Comet Assay

Tugce Yesil[1], Muzeyyen Tugce Karakas Demir[2], Merve Hidiroglu[2], Seher Karsli[1]

[1]Marmara University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Istanbul, Türkiye
[2]Marmara University, Institute of Health Sciences, Department of Pharmaceutical Toxicology, Istanbul, Türkiye

Corresponding Author: Tugce Yesil (E-mail: tugceyesil@gmail.com)

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Abstract

Introduction: Food supplements have become increasingly popular to support nutrition, improve overall health, and prevent diseases, yet their safety and efficacy remain under scrutiny due to limited regulation and inconsistent quality standards. Bromelain, a proteolytic enzyme mixture derived from pineapples, has gained attention due to its traditional medicinal uses and anti-inflammatory, antiedematous, and antithrombotic effects. This study aimed to evaluate the hepato(geno)toxicity potential of bromelain food supplement samples on human liver cell line, purchased from a pharmacy and an online retailer. In view of the increasing usage of bromelain, its promising pharmacological activities, and the limited toxicological data, the research highlights the potential risks associated with unregulated and widely accessible bromelain products, particularly those purchased online.

Methods: A colorimetric MTT (3-dimethylthiazol-2,5-diphenyltetrazolium bromide) assay was conducted to determine the IC_{50} concentrations, while the genotoxic potential of bromelain food supplement samples on human liver cell line, were evaluated using the alkaline single-cell gel electrophoresis assay (Comet Assay).

Results: No statistically significant differences in genotoxic potential were observed for either product in the HepG2 cell line when compared to the solvent control and the negative control at both tested concentrations (IC_{25} and IC_{50}).

Conclusion: Although no risks were identified for the tested products, the safety and authenticity of food supplements purchased online remain uncertain. Addressing regulatory and safety gaps requires harmonized vigilance systems, stricter marketing regulations, and increased public awareness to ensure their safe use.

Keywords: Bromelain food supplement, hepato(geno)toxicity, comet assay, MTT

1. Introduction

Food supplements are defined as “products with a determined daily intake dose prepared as capsule, tablet, lozenge, single-use powder package, liquid ampoule, dropper bottle and other similar liquid or powder forms which consist of nutrients such as vitamins, minerals, carbohydrates, fatty acids, fibers, amino acids or other physiological or nutritional effects of plant, plant and animal origin substances, bioactive substances and similar substances, alone or in mixtures, in order to supplement normal nutrition” by Turkish Food Codex Notification on food supplements (2013/49) (1).

Nowadays, due to factors such as population growth and increasing work intensity have led to disruptions in nutrition, resulting in changes of the eating habits. Consequently, food supplements have become increasingly common and popular. (2). The development of communication opportunities has raised interest in food supplements. Other factors rising this interest include people believing that supplements are natural and reliable, with no side effects, and that food supplements are easily accessible. Many people take food supplements to maintain their nutrition, stay healthy and active, and treat and prevent diseases often without consulting a health professional (3). A survey in the USA revealed that 61.2% of 376 randomly selected adults reported using food supplements. Some of these participants indicated that they used these products based on their physician's recommendation, while most stated that they obtained food supplements through friends, family, or social media (4).

The Ministry of Food, Agriculture, and Livestock licenses food supplements in Türkiye, and within the framework of the principles followed, manufacturers or importers offer the food supplements they produce and/or import to the market with the permits they receive in a very short period and through a very simple application process. There is no obligation to analyze food supplements inspected by the Ministry of Food, Agriculture and Livestock. In Türkiye, food supplements are frequently advertised across various media platforms. Their safety largely depends on the manufacturer's declaration, and the absence of rigorous safety assessments similar to those required for drugs poses a potential risk to public health. Furthermore, some products on the market are occasionally produced illegally (5). The safety of using food supplements should be questioned because they are taken in an discriminated and unregulated manner (3).

Bromelain is a mixture of proteolytic enzymes predominantly extracted from pineapples (*Ananas comosus L.*). It contains various closely related proteinases that exhibit antiedematous, anti-inflammatory, antithrombotic, and fibrinolytic activity both *in vitro* and *in vivo.* Traditionally, bromelain has been used to relieve edema, in digestive system disorders, and topically in wound and burn treatment (6). Since 1875, bromelain has been studied for its wide-ranging therapeutic benefits, including reducing blood clots, relieving conditions like angina and sinusitis, aiding recovery from injuries, and improving the absorption of medications, especially antibiotics (7, 8). Recent research also investigates bromelain's potential use in innovative treatments, suggesting it may serve as an effective drug against COVID-19 disease, as supportive and prophylactic therapy in *in vitro* or *in silico* investigations (9).

Bromelain products are available for purchase in pharmacies, markets, and through various online platforms. They are commercially available in tablet, capsule, gel, and sachet forms. Bromelain is absorbed in its active form through the gastrointestinal tract, with around 40% of the total being absorbed as its high molecular weight form. According to pharmacokinetics, the maximal blood concentration of bromelain was reached within one hour after oral dosing. Additionally, there are combined formulations of bromelain with active ingredients such as resveratrol, quercetin, curcumin, vitamin C, hyaluronic acid, and collagen. (6, 10).

Based on our observations, it is noteworthy that the edema-decreasing effect is often misinterpreted by users and bromelain food supplements are taken unintentionally to lose weight without being supported by proper diet or exercise. Additionally, consumers frequently purchase food supplements online due to their affordability. However, the safety

and authenticity of food supplements purchased through online platforms cannot be guaranteed.

The aim of this study is to evaluate the hepato(geno) toxicity of several bromelain food supplement samples on human liver cell lines, purchased from a pharmacy and an online retailer. The growing use of bromelain in recent years, the inadequacy of its toxicological studies, and its promising pharmacological activities proven by various studies served as the motivation for this work. The comet assay was employed to assess the hepato(geno) toxicity potential of bromelain food supplements in the HepG2 cell line**.**

2. Methods

2.1 Test samples

One of the bromelain food supplement samples was purchased from an online retailer (coded as e-BRM), while the other was obtained from a pharmacy (coded as p-BRM). Seven capsules (3.13 g) of the p-BRM sample and five tablets (4.9 g) of the e-BRM sample were weighed, and extracts were prepared using the maceration method with 20 mL of absolute ethanol as the solvent. The samples were mixed and left to stand overnight in the ethanol solution. The following day, they were filtered under vacuum, and this process was repeated three times. The combined filtrates were collected in a flask, and the solvent was evaporated under a vacuum at 50 °C using a rotary evaporator to obtain the extracts. A total of 0.66 g of extract (yield of 21.08%) was obtained from the p-BRM sample and 0.58 g (yield of 11.84%) was obtained from the e-BRM sample. The resulting extracts were stored at 4 °C until the day of the experiments. The extracts were solved in the culture medium with DMSO ratio fixed as 1% to reach the final concentrations in the day of the experiments.

2.2 Cell culture

The human HepG2 cells (liver cancer cell line, HB-8065; American Type Culture Collection) were incubated in 25 cm^2 flasks in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal calf serum (FCS) and 1% antibiotics (100 U/mL penicillin; 100 µg/mL streptomycin) under 5% CO_2 at 37 °C. The experiments were conducted using cells at passage numbers between 15 and 20.

2.3 Cell Viability Analysis and Dose Determination

A colorimetric MTT (3-dimethylthiazol-2,5-diphenyltetrazolium bromide) assay was performed to calculate the IC_{50} concentration, which represents the concentration at which 50% of cellular function is inhibited, indicating cell viability. A suspension of 1×10^4 cells was seeded into each well of a flat-bottom 96-well plate and incubated at 37 °C with 5% CO_2 for 24 hours to allow cell adhesion. Following the incubation period, the culture medium was removed, and the cells were exposed to the samples at final concentrations of 25, 50, 75, and 100 µg/mL (the extracts were solved in the culture medium with DMSO ratio fixed as 1%) for 24 hours to establish a dose-response curve and calculate the IC_{50} value. The culture medium was used as a negative control, while medium containing 1% dimethyl sulfoxide (DMSO) served as a solvent control. Each concentration was tested in triplicate, and controls were repeated six times. At the end of the incubation period, extraction solutions were removed, and cell viability was determined using the MTT assay, which relies on the reduction of tetrazolium salt to formazan dye by mitochondrial dehydrogenase enzymes in viable cells. Cells were incubated for 4 hours at 37 °C in 50 µL of MTT-containing medium (1 g/L), after which the resulting formazan crystals were dissolved in 160 µL of DMSO. The absorbance of the dissolved crystals was measured at 570 nm using an ELISA microplate reader, and relative cell viability (%) was calculated.

2.4 Genotoxicity

The cells were seeded into a flat-bottom 24-well plates at a density of 2×10^5 cells per well and incubated at 37 °C with 5% CO_2 for 24 hours to allow cell adhesion. Subsequently, both the e-BRM

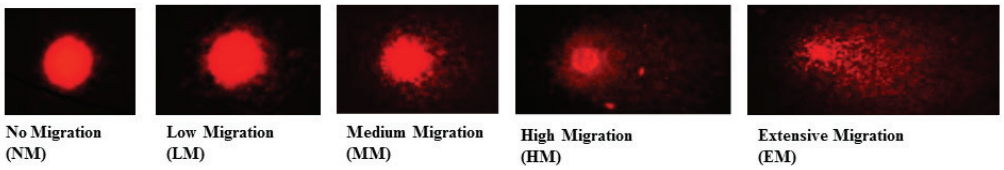

Figure 1. Comet pattern of undamaged cells to damaged cells (13).

and p-BRM samples were applied at two different final concentrations of 75 µg/mL (IC_{25}) and 100 µg/mL (IC_{50}), and the cells were incubated for an additional 24 hours. At the end of the incubation period, the extraction solutions were removed, the cells were washed with PBS, trypsinized, collected, and centrifuged 400 x g for 10 min. The supernatant was discharged, and the cell density was adjusted to $1x10^6$ cells/ml by using cold PBS.

The genotoxicity potential of e-BRM and p-BRM samples were examined by performing alkaline single cell gel electrophoresis assay (Comet Assay) according to Singh *et al*. with slight modification (11). The cells were suspended in 0.65% low melting agarose and spread onto slides pre-coated with 0.65% high melting agarose. The slides were covered with coverslips to allow the agar to solidify. After solidification, the coverslips were removed, and the slides were treated for one hour with cold lysis solution (stock lysis pH 10: 5 M NaCl, 100 mM EDTA, 10 mM Tris; freshly supplemented with 1% Triton X-100 and 10% dimethyl sulfoxide on the day of the experiment) to lyse the cells. Following the lysis stage, the experiments were carried out in a dark room. To allow the unwinding of the DNA double-strand structure in an alkaline environment, the slides were incubated in a solution containing 1 mM EDTA and 300 mM NaOH (pH > 13) for 30 minutes. Subsequently, electrophoresis was performed for 30 minutes at 15 volts and 300 mA. After this step, neutralization was carried out in three sets for a total of 15 minutes using 0.4 M Tris buffer (pH 7.5), followed by fixation of the slides with 50%, 75%, and 100% ethanol sequentially. The slides were then stained with 25 µg/mL ethidium bromide and visualized under an Olympus BX51 fluorescence microscope at 40x magnification. Damaged and undamaged cells were scored visually (Fig 1). A total of 100 cells were scored with two slides analyzed per condition. The total comet score was calculated according to following formula (12). Arbitrary Unit: 0 x No Migration (NM) + 1 x Low Migration (LM) + 2 x Medium Migration (MM) + 3 x High Migration (HM) + 4 x Extensive Migration. Figure 1 represents the microscope pattern of cells undamaged cells to damaged cells with appearance of comet. Comparisons were made with the negative control (culture medium), solvent control (1% DMSO) and positive control (100µM H_2O_2). All samples were tested in triplicate.

2.5 Statistics

Total comet scores (TCS) were expressed as the mean and standard deviation of the mean (n=3). Statistical analyses were conducted using the SPSS 20.0 software. The normality of the distribution continuous variables was tested by Shapiro–Wilk's test. Since the distribution was found to be normal, the means of the results obtained from three replicates (n=3) at different concentrations were compared using (ANOVA), with a Tukey multiple comparison, post hoc test for comparisons of different treatments versus the respective controls. Statistical significance was considered for $p<0.05$.

3. Results

The percentage of cell viability after 24 hours of exposure to increasing concentrations is shown in Figure 2. A proportional decrease in cell proliferation was observed with increasing concentrations of the e-BRM sample. However, no dose-dependent linear response was detected for the p-BRM sample. The IC_{25} and IC_{50} values for the e-BRM sample were calculated as 76.45 µg/mL and 103.48 µg/mL, respectively. Based on these results, the *in vitro* alkaline comet assay was performed at two different final concentrations (75 and 100 µg/mL) for both samples, with each condition tested in triplicate.

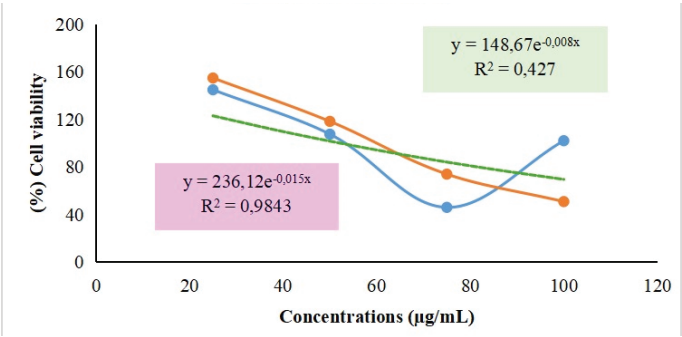

Figure 2. Percentage of the HepG2 cell viability after 24-hour incubation with different concentrations of bromelain food supplement extract samples

The mean TCS values of the samples are presented in Table 1. When comparing the genotoxic potential of both products in the HepG2 cell line with the solvent control and the negative control, no statistically significant differences were observed at either concentration (75 or 100 µg/mL) for both samples. However, the positive control showed a statistically significant difference in terms of its potential to cause genotoxic damage.

Table 1. Mean TCS Values After Sample Applications in the HepG2 Cell Line

Sample (n=3)	Final Concentrations	Total Comet Score (mean±SD) TCS±SD
Negative control	0	3,79 ± 0,96
Solvent control (DMSO)	%1	7,44 ± 0,94
Positive control (H_2O_2)	100 µM	182,71 ± 62,91***
e-BRM	75 µg/mL	6,49 ± 4,26
	100 µg/mL	4,73 ± 1,99
p-BRM	75 µg/mL	8,68 ± 2,89
	100 µg/mL	6,67± 2,12

Total comet score (TCS): 0 x No Migration (NM) + 1 x Low Migration (LM) + 2 x Medium Migration (MM) + 3 x High Migration (HM) + 4 x Extensive Migration (EM). a Significance of positive control compared with each sample at * p< 0.05; ** p<0.005; *** p<0.001.

4. Discussion

Food supplements (FSs) are increasingly popular but pose global regulatory and safety challenges due to inconsistent product quality, misleading marketing, and gaps in post-market surveillance (14). Furthermore, manufacturers are not obliged to disclose potential with other substances, alcohol, and medicinal products (15). Internet marketing exacerbates these issues by enabling cross-border distribution that bypasses regulations. In the U.S., over half of plant food supplements (PFSs) feature misleading labels, claiming to treat diseases like diabetes, heart disease, and cancer despite regulatory bans. Similarly, the FDA has recorded numerous instances of deceptive marketing. In Europe, unauthorized claims also mislead consumers, creating risks tied to unclear product efficacy (14). Regulatory systems for FSs differ between regions. The European Food Safety Authority (EFSA) provides guidelines, but the absence of centralized post-market vigilance leaves gaps. Only a few countries, such as France and Denmark, have dedicated nutrivigilance systems relying on voluntary reporting (16, 17). In Türkiye, although a centralized vigilance system monitors the medicinal products, there is no centralized vigilance system for food supplements, which may have a risk for monitoring the safety profile of food supplements (18). The complexity of assessing adverse drug reactions (ADRs) further complicates the evaluation of FSs safety. Challenges include the lack of diagnostic markers for herb- and drug-induced liver injuries (HILI/DILI) and inconclusive *in vitro* studies on toxicity and bioavailability. The interplay of these challenges emphasizes the necessity for more robust regulatory frameworks and mandatory pre-market safety studies for PFSs (14).

Numerous studies investigated the potential beneficial properties (9), while only few studies previously focused on the safety and toxicity of bromelain or bromelain supplements. The preclinical toxicity studies, especially LD50 studies, were published before the 1980s, and neither abstracts nor full texts of these studies are available online. Therefore, according to the review articles citing these older studies, generally describe bromelain as an acutely safe and well-tolerated phytochemical compound (19, 20).

According to the World Health Organization's (WHO) VigiAccess database, 1285 adverse drug

reactions (ADRs) have been reported for bromelain-containing products in the post-marketing period since they were first marketed, and a trend of increasing reported ADRs has been observed since 2018. Gastrointestinal disorders; general disorders such as oedema and pain; nervous system disorders such as dizziness, somnolence and headache; skin and subcutaneous tissue disorders such as pruritus, rash, and urticaria were the most frequently reported ADRs on bromelain-containing products. Eight of 1285 ADRs were related hepatobiliary disorders, including acute/chronic hepatic failure, cholecystitis, hepatitis, drug-induced liver injury (DILI), abnormal hepatic function, jaundice, and portal vein thrombosis. Also, elevated transaminase enzymes levels were recorded in the database. ADRs have been reported the most frequently in Asia, subsequently in Europe (21). To minimize adverse effects when taking food supplements, it is critical to consider the requirements of the user, diseases, regularly used medications, even medications prescribed for acute illnesses.

Drug interactions are often ignored in the use of bromelain food supplements. However, studies have shown that bromelain can increase the plasma concentration of antibiotics and has an anticoagulant effect (22). Also, four ADRs related to drug interactions for bromelain-containing products have been recorded in the VigiAccess database (21). On the other hand, exposure to bromelain via inhalation has been associated with asthma and IgE-mediated allergic reactions in a few case studies (23, 24).

Since the liver is the primary target organ for substances entering systemic circulation and plays a central role in metabolism, as well as the bioactivation and detoxification of compounds, the liver models are essential for toxicity testing. Primary human hepatocyte cultures are considered the gold standard for such studies; however, they have notable limitations, including donor variability, high culturing costs, and isolation challenges. As an alternative, the human hepatocellular carcinoma cell line HepG2 is widely used in toxicology and cancer research. HepG2 cells offer several advantages, such as being of human origin, ease of availability, the ability to produce highly reproducible results, and a limited but functional metabolic capacity (25). For this reason, HepG2 cells were selected in our study to determine hepato(geno)toxicity potential of the selected bromelain food supplements.

The cytotoxic and anticancer properties of bromelain were investigated in various carcinoma cell line (26, 27, 28, 29). Murthy et al. treated HepG2 cells with bromelain at concentrations of 25 µg/mL, 50 µg/mL, 100 µg/mL, and 125 µg/mL for 24, 48, and 72 hours, demonstrating a decrease in cell viability in a concentration-dependent manner. The IC_{50} value of bromelain for 24 hours was reported as 1.35µM (approximately 44.55 µg/mL) (29). In our study, although a proportional decrease in cell proliferation was observed with increasing concentrations of the e-BRM sample, the p-BRM sample did not exhibit a dose-dependent linear response. The IC_{25} and IC_{50} values for the e-BRM sample were determined to be 76.45 µg/mL and 103.48 µg/mL, respectively. The IC_{50} value in our study was higher than the result reported by Murthy *et al*. In fact, direct comparison between the two studies may not entirely appropriate, as our study focused on evaluating the effects of bromelain extracted from a food supplement on cell proliferation, whereas the other study utilized pure bromelain samples.

To the best of our knowledge, no studies have investigated the genotoxicity of bromelain food supplement products. In our study, no statistically significant differences in genotoxic potential were observed for either product in the HepG2 cell line when compared to the solvent control and the negative control at both tested concentrations (75 and 100 µg/mL).

5. Conclusion

No hepato(geno)toxic effects were observed for either product. While this study does not indicate a risk associated with the tested products, the safety and authenticity of food supplements purchased through online platforms cannot be guaranteed. In summary, although PFSs are widely marketed and consumed, significant regulatory and safety gaps are present. Addressing these challenges requires the

implementation of harmonized vigilance systems, stricter marketing regulations, and increased public awareness to ensure the safe use of FSs and mitigate potential health risks.

Conflicts of interest: The authors declare no conflicts of interest related to this work.

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Ethics approval: Not applicable

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