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THE PROTECTIVE AND ANTI-INFLAMMATORY EFFICIENCY OF LYOPHILIZED BLUEBERRY AND STRAWBERRY POLYPHENOLS ON EXPERIMENTALLY INDUCED GASTRIC ULCER IN RATS

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ABSTRACT

This study examined the gastro protective effects of lyophilized blueberry and strawberry polyphenols against gastric ulcer induced by indomethacin in rats. The administration of indomethacin significantly increased the ulcer index associated with increased antioxidant, inflammatory, and gastrointestinal examination parameters and decreased SOD and GSH, while the rats treated with both blueberry and strawberry in combination had the lowest ulcer index and the maximum value for ulcer preventive index. Treatment with blueberry and/or strawberry efficiently reduced gastric injury, oxidative stress and proinflammatory cytokines and demonstrated a hopeful role against gastric ulcer.

Keywords: Polyphenols, Indomethacin, Gastric Ulcer, Blueberry, Strawberry, Inflammation

INTRODUCTION

Gastric ulcers represent a significant category of gastrointestinal disorders that are receiving worldwide interest in the medical field **Wang *et al.*, (2023)**. Globally, about 4 million people suffer from stomach ulcers. Ten to twenty percent of this would result in complications **Xie *et al.*, (2019)**. Severe stress, alcohol use, and non-steroidal anti-inflammatory drug use are major risk factors for stomach **ulcers (Otumo et al., 2024)**. These factors, which include elevated pepsin and gastric acid secretion, reduced gastric perfusion, inhibited prostaglandin synthesis, altered gastric mobility, and inhibition of mucosal cell proliferation, have been found to play a significant role in the development of gastric ulcers. Additionally, studies indicate that the general pathophysiology of stomach ulcers is significantly influenced by the production of oxygen free radicals **Li *et al.*, (2013)**. NSAIDs reported for around 10% of the highest prescribed medicines **Wongrakpanich *et al.*, (2018)**. They are frequently used to treat pain and inflammation because of their potent analgesic, antipyretic, and anti-inflammatory qualities **Bosch *et al.*, (2022)**. However, their severe adverse effects—particularly gastrointestinal ulcers, renal damage, and cardiovascular thrombotic events—hinder their widespread clinical use **Bindu *et al.*, (2020)**.

Berries are small, fleshy, commercially grown fruits, like strawberries, blueberries, blackberries, cranberries, black raspberries, and red raspberries, which are available in both fresh and processed varieties **Raudone *et al.*, (2021)**. The phytochemicals found in berries, particularly phenolic compounds, are abundant. These substances contribute to a number of health benefits linked to berry fruits, including anti-inflammatory, antibacterial, anticancer, and antioxidant properties **(Lavefve *et al.*, 2020)**. Berries are known to be a rich source of flavonoid compounds, especially anthocyanins, which give these fruits their blue, purple, and red hues and high level of popularity **Cosme *et al.*, (2022)**. These pigments have been considerably studied for their possible bioactivity in the human body and have strong antioxidant effects **Bouyahya *et al.*, (2022)**.

Blueberry is one of the most well-known fruits with high anthocyanin content, a significant polyphenolic group of substances known for its nutritive and health-promoting properties **Yang *et al.*, (2022)**. They are also said to have antidiabetic, antimicrobial, and anticarcinogenic qualities **Kalt *et al.*, (2020)**. According to reports, blueberries have one of the highest TACs of any fruit to date and contain polyphenols including anthocyanins, phenolic acids, tannins, and flavanols **(Olas, 2018)**. Blueberry anthocyanins have been shown to reduce oxidative and inflammatory damage to the endothelium by inhibiting the production of inflammatory mediators **Del Bo *et al.*, (2022)** as well as to have preventive health effects **(Curtis et al.,2022)**. As a result, blueberries and their derivatives are widely used in a variety of meals. Both fresh and frozen fruits are consumed, and they are also used as ingredients in baked goods, fruit fillings, canned goods, preserves, syrups, juices, drinks, food coloring, and beverages **Tobar-Bolanos *et al.*, (2021)**. Strawberry, the most significant fruit among these widely consumed berry varieties. The spherical, dark red, and delicious strawberry is a native Mediterranean fruit that is also grown in other parts of Eastern Europe **(Bilwali et al., 2021)**. In addition to being eaten fresh, these fruits are primarily consumed in processed forms such jellies and jams **Pallauf *et al.*, (2008)**. In traditional medicine, these substances which are abundant in carotenoids, vitamin E, vitamin C, and phenolic compounds, particularly anthocyanin—are used as antiseptics, diuretics, laxatives, and to treat diabetes and hypertension **Bnouham *et al.*, (2007).** Strawberries contain a variety of phytochemicals, including procyanidins, ellagitannins, and anthocyanins, which the body absorbs and metabolizes to create various phenolic conjugates and metabolites that lower the risk of disease **Bader *et al.*, (2022)**.

There are reasons to believe that blueberries and strawberries may have positive protective effects, reducing oxidative stress and inflammation in gastric ulcerative rats, even though no studies have tested the effects of supplementing these berries in patients with gastric ulcers. This is especially true given the current interest in determining the potential benefits of medicinal plants, such as blueberries and strawberries. Therefore, this study was designed to be a novel study to evaluate the protective effect of freeze-dried blueberries and strawberry polyphenols against gastric ulcer in rats.

MATERIALS AND METHODS

Berries and chemicals

Freeze dried blueberry and strawberry were purchased as dietary supplements from Natierra Superfoods, Vân Nuys, California, USA. Indomethacin was bought from Nile Company for Pharmaceutical and Chemical, Cairo, Egypt.

Ethical consideration

This work was authorized by the Sciences Academy of Experimental Research's Ethics Committee in Egypt [28 Oct 2024, No. 44713].

Experimental animal

Fifty adult male Sprague-Dawley albino rats weighing between 118 and 132 g were used in this investigation. Following a week of acclimation, the animals were placed in groups and kept in climate-controlled settings (23 ± 2 C, 47% humidity). A basal diet through the experimental period **Reeves *et al.*, (1993)**.

Ulcer induction

Using the method described by **Sayanti *et al.*, (2007)**, gastric ulceration was induced in experimental rats. In short, rats were given 30 mg indomethacin /kg b.w orally as a single dosage. Twenty-four hours before the ulcer was induced, they were given free access to water only without diet.

Design for experiments

The rats were split up into the following five groups of ten:

I: Normal control; Fed on basal diet.
II: Ulcerated control (IND); A single oral dose of indomethacin (30 mg/kg b.w.) was given to rats fed a basal diet.
III: Blueberry (BB+IND): Fed a basal diet supplemented with 2 g freeze dried blueberry powder /100 g diet for 28 prior to indomethacin administration.
IV: Strawberry (SB+IND): Fed a basal diet supplemented with 2 g freeze dried strawberry /100 g diet for 28 days prior to indomethacin administration.
V: Blueberry+ Strawberry (BB+SB+IND): Fed a basal diet supplemented with 2 g freeze dried blueberry and 2 g freeze dried strawberry /100 g diet for 28 days prior to indomethacin administration.

Blood sample collection and isolation of stomach

Diethyl ether anesthesia was used to sacrifice the animals on the last day, (4 h post ulcer induction), and blood was drawn via retro-orbital puncture. After allowing the blood to settle for 30 minutes at 25°C to separate the serum, it was centrifuged for 20 minutes at 5000 rpm, separated into multiple aliquot part, and kept at -22°C until analysis. Following laparotomy, the stomach was excised and subsequently opened along with the greater curvature. The gastric contents were collected and transferred into a centrifuge tube. After the addition of 5 mL of distilled water, the mixture was centrifuged at 3000 rpm for 10 minutes. The emptied and rinsed stomachs were then stored in 0.1 M phosphate buffer prior to homogenization and microscopic examination.

Macroscopic examinations (Assessment of gastric mucosal lesions)

After being opened, gastric were cleaned with saline solution and checked for glandular lesions. Extent of ulceration was measured according to **Szabo and Hollander, (1985)**. The results are shown in Table 1 and indicate the extent of hemorrhagic erosions, lesions, and vascular congestions. Each rat's ulcer score was converted to an ulcer index (U.I.), and the expressions were used to calculate the percentage of ulcer prevention.
The efficiency of treatments (BB and SB) was determined by applying the formula: Ulcer protective index (%) = Ulcer index of ulcerated control - Ulcer index of treated/Ulcer index of ulcerated control % **Kumar *et al.*, (2013)**.

Table 1 Scores for ulcers and a description

Score	Remark
0	Normal mucosa
1	Vascular congestion
2	One or two lesions
3	Severe lesions
4	Very severe lesions
5	Mucosa full of lesions

Preparing a gastric tissue homogenate for biochemical analysis

A tissue homogenizer was used to homogenize about 1 g of stomach tissue in 1 ml of phosphate buffered saline. After centrifuging the homogenate for 10 minutes at 10,000 rpm, the supernatant was collected and kept for further examination.

Gastric tissue Analysis

Spectrophotometric measurements of reduced glutathione (GSH), xanthine oxidase (XO), malondialdehyde (MDA), and superoxide dismutase (SOD) were performed in duplicate using Biovision kits, CA, USA.

Serum Analysis

TNF-α, IL-6, and NF-κB were measured using an enzyme-linked immunosorbent test kit (Kamiya Biomedical Co. CA, USA). Prostaglandin E2 (PGE2) was measured using a kit bought from Biodiagnostic Co. Ltd. Cairo, Egypt. The enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of caspase-3 and 8-hydroxy-2deoxyguanosine (8-OHdG) in serum performed in duplicate using a kit obtained from the Bioassay Technology Laboratory, China.

HISTOPATHOLOGY

Samples of gastric tissue were sectioned, deparaffinized, and stained with hematoxylin and eosin after being preserved in a 10% formalin solution.

STATISTICAL ANALYSIS

The statistical software SPSS version 21.0 was used to examine the data. The findings were displayed as mean ± standard deviation. Analysis of variance (ANOVA) and least significance (LSD) tests were used to ascertain the differences between mean values. It was considered significant when $p \leq 0.05$.

RESULTS

When indomethacin was administered to the ulcerated control group, the ulcer index increased considerably ($p \leq 0.05$). In contrast, the groups with the least number of ulcers were BB (Group III), SB (Group IV), and BB+SB (Group V). The estimated ulcer index (Figure 1) established that the rats in the ulcerated control group had the greatest ulcer index of (4.60 ±0.35) but the rats treated with both blueberry and strawberry (group V) had the lowest (0.41 ± 0.05). Similarly, group V, which received a combination of strawberry and blueberries, had the greatest ulcer prevention index value (91.08%), followed by groups III (84.88%) and IV (74.44%) (Figure 1).

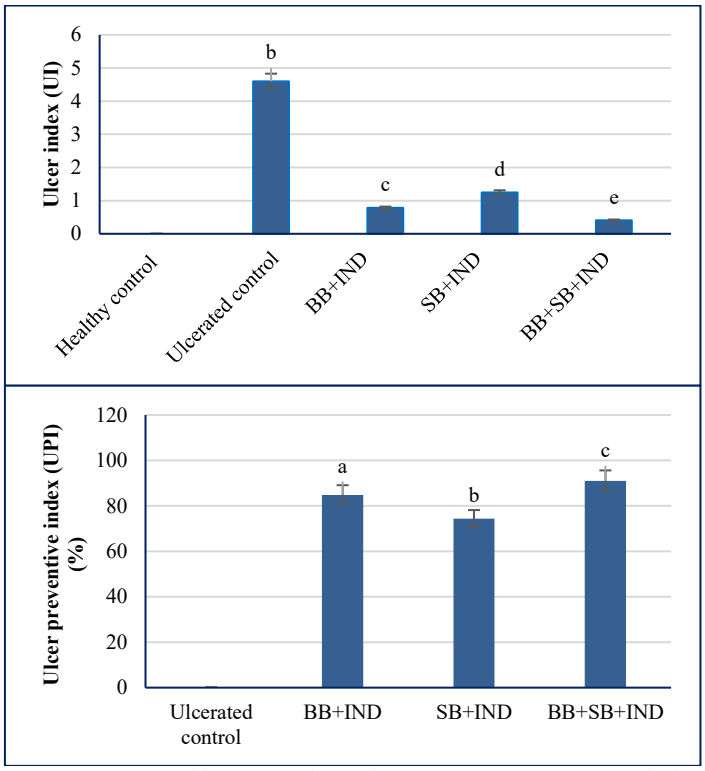

Figure 1 Effect of blueberry and strawberry on ulcer index (IU) and ulcer preventive index (UPI). Significant differences ($p \leq 0.05$) are shown by bars with distinct superscripts for the parameter. BB: blueberry, SB: strawberry; IND: indomethacin.

A considerable increase ($p \leq 0.05$) in MDA and XO values and a substantial drop in gastric SOD and GSH enzyme activities as compared to the healthy group are indicative of indomethacin-induced oxidative stress. All treated groups' levels of oxidative stress indicators were significantly reduced by blueberry and strawberry treatment. The remarked effects compared well with healthy control rats, and diets supplemented with a mixture of BB and SB produced a substantial improvement in these parameters.

Table 2 Effect of indomethacin, blueberry, and strawberry on oxidative stress markers

Groups	SOD (U/g tissue)	MDA (U/g tissue)	GSH (U/g tissue)	XO (U/g tissue)
Healthy control	14.2 ^{a} ±0.16	4.75 ^{a} ±0.03	5.22 ^{a} ±0.30	42.9 ^{a} ±3.06
Ulcerated control	6.7 ^{b} ±0.08	8.15 ^{b} ±0.05	2.60 ^{b} ±0.23	75.5 ^{b} ±6.03
BB+IND	12.2 ^{c} ±0.04	5.82 ^{c} ±0.08	4.80 ^{c} ±0.70	52.1 ^{c} ±4.30
SB+IND	10.5 ^{d} ±0.05	6.66 ^{d} ±0.09	3.54 ^{d} ±0.10	59.1 ^{d} ±6.50
BB+SB+IND	13.8 ^{a} ±0.05	4.97 ^{a} ±0.01	5.09 ^{a} ±0.52	40.6 ^{a} ±3.15

Values are illustrated as mean +/- standard error (n = 10, X ± SEM). IND: indomethacin. BB: blueberry, SB: strawberry. Substantial differences ($p \leq 0.05$) exist amongst means for the parameter with various superscripts.

Effect of different treatments on apoptotic biomarkers

Figures 2 elucidate the effect of indomethacin, blueberry, and strawberry on serum biomarkers of DNA damage; 8-hydroxy-2deoxyguanosine (8-OHdG) and apoptotic marker; caspase3 (CASP3). The data shown manifest that indomethacin administration

increased 8-OHdG marker of oxidative destruction of DNA and significant versus control and all other groups. Blueberry alone or in combination with strawberry treated groups showed significant decrease($p \leq 0.05$) in 8-OHdG in serum. On the other hand, results of serum caspase-3 biomarker revealed that indomethacin group (ulcerated control) induce remarkable increase in caspase-3 level 66.67% from control and significant versus all other treated groups. The marked decrease in serum caspase-3 in BB, SB and Mix treated groups was detected and significant versus healthy and ulcerated control rats.

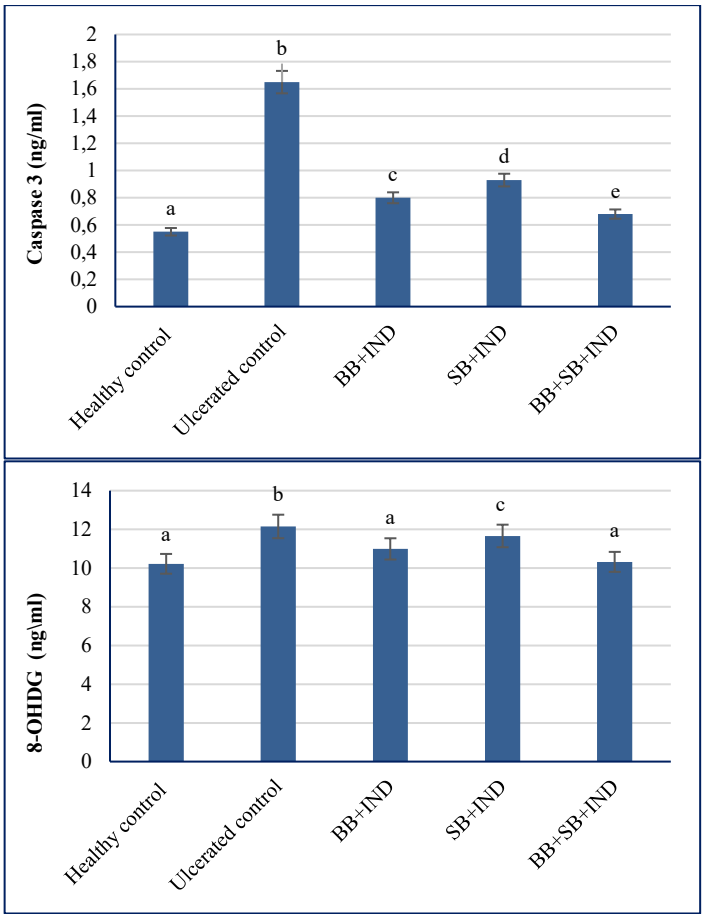

Figure 2 Effect of different treatments on serum apoptotic markers. IND: indomethacin. BB: blueberry, SB: strawberry. Significant differences ($p \leq 0.05$) are shown by bars with distinct superscripts for the parameter. BB: blueberry, SB: strawberry; IND: indomethacin.

The effects of various treatments on serum inflammatory indicators are displayed in Table 3. When compared to the healthy control group, indomethacin induced a considerable decrease ($p \leq 0.05$) in PGE2 levels and a substantial increase in NF-kB, TNF-α, and IL-6 indicating a powerful inflammatory response. Supplementation of strawberries or blueberries, however, significantly ($p < 0.05$) reduced the levels of inflammatory biomarkers.
Rats fed diets supplemented with both strawberries and blueberries (group V) showed the greatest decrease in inflammatory biomarker levels when compared to other treatment groups.

Table 3 Effect of indomethacin, blueberry, and strawberry on levels of inflammatory markers

Groups	NF-kB (pg\ml)	IL-6 (pg/ml)	TNF-α (pg/ml)	PGE2 (pg/ml)
Healthy control	60.15 ^{a} ±5.3	146.22 ^{a} ±5.07	32.80 ^{a} ±3.86	301.0 ^{a} ±7.8
Ulcerated control	85.15 ^{b} ±8.2	265.45 ^{b} ±7.20	80.65 ^{b} ±5.08	125.6 ^{b} ±6.3
BB+IND	69.30 ^{c} ±3.5	200.00 ^{c} ±4.55	52.80 ^{c} ±2.73	275.5 ^{c} ±8.5
SB+IND	72.52 ^{c} ±3.3	178.7 ^{d} 3±3.75	49.40 ^{c} ±3.80	245.6 ^{d} ±5.6
BB+SB+IND	64.30 ^{a} ±2.5	160.75 ^{e} ±5.70	35.65 ^{a} ±2.55	293.0 ^{e} ±3.5

Values are shown as mean +/- standard error (n = 10, X ± SEM). IND: indomethacin. BB: blueberry, SB: strawberry. Substantial differences ($p \leq 0.05$) exist between means for the parameter with various superscripts.

Stomach slices from healthy rats revealed a normal gastric mucosa (Fig. 3-a), in contrast to the ulcerated animals (G2), which showed significant inflammation and vascularization associated with destructions of the stomach mucous membrane (Fig. 3-b). Supplementation diets with blueberries (Fig. 3-c) improved the histological changes induced by indomethacin, according to a comparison of treatment groups. Additionally, gastric erosion was lessened when strawberries were used as a protective agent (Fig. 3d). The results indicated that indomethacin-induced stomach lesions were improved by supplementing blueberries either alone or in combination with strawberries (Fig. 3e).

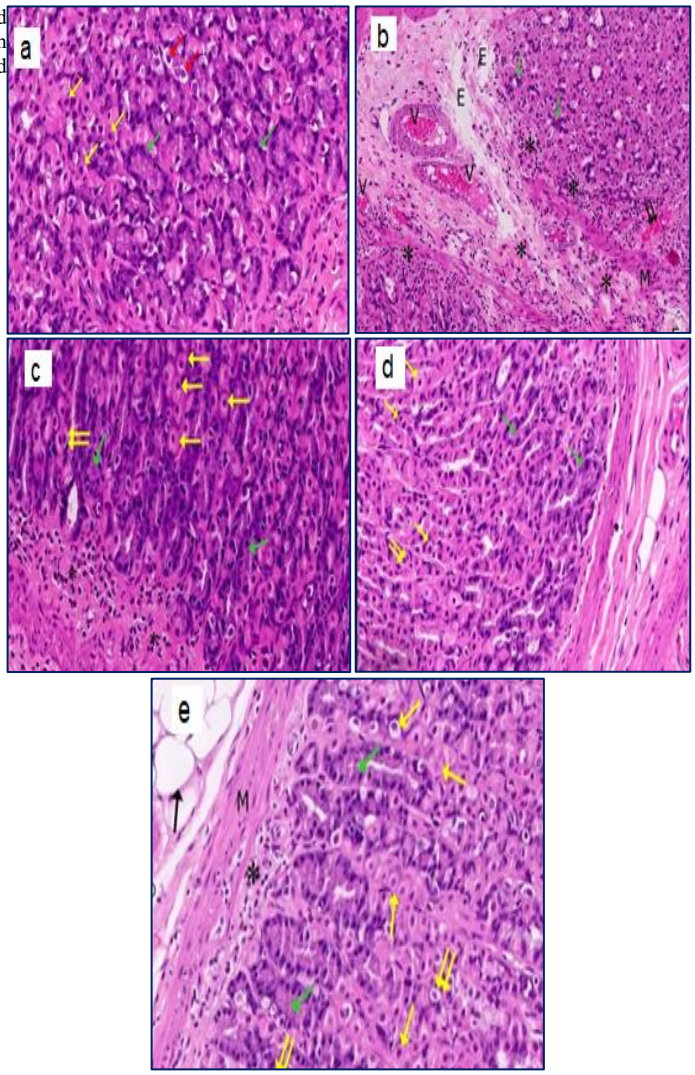

Figure 3 Effect of indomethacin, blueberry, and strawberry on Histological examination of stomach tissue. **a:** healthy control; showed normal gastric mucosa. **b:** ulcerated control; showing the floor of the ulcer and some of the chief cells are lost, extravasated red blood cells (↑↑), mononuclear inflammatory, cellular infiltrations, and disorganized muscularis mucosa. **c:** blueberry treatment; showing continuous basic part of the fundic gland with the inflammatory cells in lamina propria. **d:** strawberry treatment; showing the basal part of fundic glands are lined by many low columnar chief cells with basal nuclei and basal basophilic cytoplasm (green ↑). Notice large parietal cells (yellow ↑) with acidophilic cytoplasm and central rounded vesicular nuclei. **e:** blueberry and strawberry in combination treatment; showing an apparent decrease in the number of parietal cells, some appear with vacuolated cytoplasm and decrease of inflammation.

DISCUSSION

Gastric ulcer still among the most common diseases impacting 5–10% of the general population despite the availability of several therapeutic options, including antacids, proton pump inhibitors, and mucosal barriers **Kavit *et al.*, (2019)**. Indomethacin, like other NSAIDs, causes gastric mucosal ulcers by pharmacologically blocking the cyclooxygenase (COX) enzyme, decreasing the production of gastro-protective prostaglandins, lowering mucosal blood flow and epithelial cell renewal, and increasing acid back diffusion. Indomethacin has demonstrated prostaglandin-independent effects that are arbitrated by increases in reactive oxygen species, pro-inflammatory mediators, and neutrophil infiltration of the stomach tissue, ultimately leading to gastric damage and apoptosis **Zhou *et al.*, (2020)**. The current study's findings demonstrated that indomethacin resulted in severe stomach ulcers, which is consistent with earlier research **El-Ashmawy *et al.*, (2016)**.
Berries have drawn more attention since they contain a wide range of bioactive substances, including polyphenols (anthocyanins, phenolic acids, tannins, and carotenoids). Strawberries are prominent among these berries due to their abundance of bioactive substances like polyphenols, phenolic compounds, flavonoids, anthocyanins, and hydroxycinnamic acid derivatives. Because of their

antioxidant qualities and cooperative effect on promoting human health and preventing disease, these chemicals are of growing importance. Likewise, anthocyanins and phenolics are more abundant in blueberries **Bader *et al.*, (2021)**. Gastric mucosal walls were significantly protected against hemorrhagic ulcerations when the rats were pretreated with blueberries or strawberries 28 days before indomethacin was used to induce ulcers. When compared to group II, which received only indomethacin without any pretreatment, the animals in groups III, IV, and V showed a statistically significant ($p \leq 0.05$) drop in mean ulcer index, indicating this protection. The experimental rats were protected to varying degrees from indomethacin-induced stomach ulcers by the blueberry and strawberry, according to calculated percentage ulcer protective indices for treatment groups III through V.

Berries have anti-ulcer properties that include reducing the production of acid, inhibiting the activity of pepsin, and promoting the secretion of gastric mucus and bicarbonate. Additionally, berries improve the mucosal defenses against gastric ulcers by strengthening their antibacterial, anti-inflammatory, antioxidative, and cytoprotective properties **Zhang *et al.*, (2020).** It has been demonstrated that using strawberries and blueberries, either separately or in combination, decreased the incidence of gastric ulcers. Previous research has demonstrated a substantial correlation between a diet that includes vitamins, dietary fibers, and beneficial biological active substances, particularly effluents in fruits and vegetables, and a variety of morphologies associated with inflammation **(Gasparrini *et al.*, 2017; Raudone *et al.*, 2021)**

The current study's findings demonstrated that berries, including blueberries and strawberries, could prevent the damage induced by indomethacin. This suggests that berries provide a gastroprotective effect through a mechanism that is independent of PGs and most likely involves anti-inflammatory and free radical scavenging properties **(Sangiovanni *et al.*, 2017; Serafin *et al.*, 2020)**. The antioxidant and bioactive qualities of blueberries are primarily attributed to anthocyanins, which make up between 35 and 74% of all phenolic compounds. Flavonoids' antioxidant qualities are associated with their health advantages; multiple studies have shown that these phytochemicals may absorb reactive oxygen species **(Qiao *et al.*, 2024; Pap *et al.*, 2021).** Flavonoids also could stabilize membranes **(Kumar and pandey, 2013).**

The results of the current study showed that blueberry and strawberries preserved the gastric mucosal oxidative stress biomarkers (GSH, MDA, XO, SOD). As strong antioxidants, flavonoids help prevent stomach ulcers by scavenging free radicals and reducing their production. In addition to directly scavenging ROS, flavonoids also shield and activate antioxidant enzymes, preventing oxidative damage in stomach ulcers **Reuter *et al.*, (2010).** Blueberry anthocyanins have been shown to have other positive effects in addition to their antioxidant properties. For example, a few mechanistic studies have proposed that blueberry polyphenols may have anti-inflammatory and antioxidative properties **Maya-Cano *et al.*, (2021).** It is well recognized that excessive ROS production results in lipid impairment, DNA and protein damage, and abnormalities in cell function **Johnson *et al.*, (2017)**. Consuming berries, particularly blueberries, is positively associated with a lower risk of stomach ulcers **Shu *et al.*, (2022)**. Initially, this effect was thought to be caused by vitamins and carotenoids due to their antioxidant properties **Del Bo *et al.*, (2022).**

The current study's findings showed that indomethacin increased pro-apoptotic signaling molecules, particularly caspase-3, a crucial pro-apoptotic executor. According to our research, pretreatment with strawberries and blueberries significantly reduced serum levels of the apoptotic marker caspase-3 and DNA damage biomarker 8-OHdG. According to previous clinical research, blueberries are thought to be the most significant edible variety of berries, possessing a diversity of bioactive properties, including anti-inflammatory, antioxidant, and anti-ulcer properties. Blueberries accomplish their anticancer function via lowering DNA damage and the growth of cancer cells **(Folmer *et al.*, 2014; Rasool, 2012)**. Although phenolic chemicals found in strawberries are well known for their anti-inflammatory and antioxidant properties, recent research has shown that their bioactivities extend to a number of additional pathways, such as cellular development and survival **Newerli-Guz *et al.*, (2023).**

Recent studies have shown that pre-treating cells with strawberries after lipopolysaccharide treatment reduces the rate of apoptosis, the amount of reactive intracellular oxygen species, improves mitochondrial function, and strengthens the cells' ability to fight cancer. These defensive biological activities of strawberries are caused by suppression of the NF-kB signaling pathway and stimulation of the cellular antioxidant defense systems **Raque *et al.*, (2014).** One of the most important roles of macrophages during the inflammatory response is the release of various inflammatory cytokines, including interleukin (IL-6), tumor necrosis factor (TNF)-α, and inflammatory mediators **Peng *et al.*, (2022)**. Targeting and controlling these pro-inflammatory cytokines and mediators may be crucial to preventing many diseases linked to inflammation since their prolonged excessive production can cause inflammation, DNA damage, and cancer. Through the manipulation of relevant pathways and the management of the proportion of cellular anti-inflammatory cytokine production, the current study results demonstrated the medicinal efficiency of strawberries and their phenolic components toward anti-inflammatory activity. The study's macroscopic and histologic findings showed that strawberries and blueberries had a strong gastroprotective effect against stomach ulcers brought on by indomethacin. The results indicated that indomethacin-induced stomach lesions were improved by supplementing blueberries either alone or in combination with strawberries. This is consistent with other findings that showed strawberry tannins as components of nutraceuticals with possible anti-gastritis capabilities **Da Silva *et al.*, (2020)** and the gastroprotective action of blueberry extract against ethanol-induced gastric ulcer in rats **Jacob *et al.*, (2024).**

CONCLUSION

In conclusion, bioactive substances, primarily anthocyanins, are abundant in blueberries and strawberries. These substances are antioxidants and have a great chance of preventing a number of diseases, including gastric ulcers, inflammation, and several associated problems. These biological uses have made it possible to use berries and their bioactive ingredients in medicines, nutraceuticals, and nutritional supplements as well as in the food and pharmaceutical industries.

Availability of data and materials: The data sets used in this study are available with the corresponding author and will be provided on a reasonable request.

Competing interest: The authors have no conflict of interest to declare.

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