Research article

Gastroprotective effects of *Triticum aestivum* Linn., extract on ethanol-induced gastric ulcer in Wistar rats

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ABSTRACT

Introduction and Aim: *Triticum aestivum* (wheatgrass) is high in nutrient availability and antioxidant enzymes. It also functions as a detoxifier and aids in the rejuvenation of healthy cells. The current study sought to determine the gastroprotective impact of aqueous ethanolic extract of wheatgrass on the ethanol-induced gastric ulcer.

Materials and Methods: Wistar rats were given an oral dosage of 100% ethanol (1 ml/200g) to cause gastric ulcers. A reference medicine called omeprazole was given orally at dosages of 20 mg/kg body weight and 200 and 400 mg/kg of wheatgrass extract, respectively. Blood samples were taken an hour after ethanol administration, and the stomachs of deceased rats were then examined biochemically, macroscopically, and microscopically.

Results: The gastric ulcer index considerably decreased after taking wheatgrass extract orally, which showed a considerable attenuation of gastric ulcer. The serum level of TNF-α and the activity of the gastric MPO were both significantly enhanced by pre-treatment with wheatgrass extract. Furthermore, compared to the ethanol-induced group, wheatgrass pre-treatment dramatically boosted gastric levels of enzymatic and non-enzymatic antioxidants, including CAT, TAC, and GSH with concurrent reductions in MDA levels. Further evidence for these conclusions came from histopathology research, which showed that wheatgrass had a healing impact on the hemorrhagic shock brought on by ethanol poisoning.

Conclusion: Due to its propensity to decrease oxidative stress and gastric inflammation, wheatgrass extract may have gastroprotective effects on ethanol-induced stomach ulcers.

Keywords: Wheatgrass; gastric ulcer; antioxidants; Wistar albino rats; biochemical parameters.

INTRODUCTION

A benign lesion known as a gastric ulcer has several aetiologies and is caused by an imbalance between the mucosal epithelium's protective gastric components and its aggressive physical, chemical, or psychological forces (1). Physical stress, heavy cigarette use, alcohol or caffeine use, some types of medicines, especially non-steroidal anti-inflammatory drugs, and Helicobacter pylori infection are among these aggressive variables (2). High alcohol intake is one of these elements that damage the stomach mucosa the most. In order to screen the anti-ulcer drugs, the experimental model of ethanol-induced stomach ulcer is frequently used (3).

Despite the fact that pharmaceutical drugs predominate in the treatment of the majority of human illnesses, including stomach ulcers, traditional medicine is still widely practised today. The high incidence of side effects, pharmaceutical interactions, and germ resistance, as well as the exorbitant expense of chemical therapy, may all contribute to this (4). As a result, it's essential to switch out chemical medications with natural ones that have a variety of biological activities, increased efficacy, and safer profiles (5). Research on herbal items with pharmacological properties is urgently needed in order to discover alternative bioactive phytocompounds (6).

Triticum aestivum Linn., sometimes known as wheatgrass, is a member of the Gramineae family and is grown extensively all over the world. Usually, wheat that germinated over a period of 6 to 10 days is referred to as "wheatgrasses." The process of germination or sprouting causes the seeds to go through substantial changes. At this stage, the synthesis of healthy compounds including vitamins and phenolics begins. It is commonly referred to as "green blood" due to the significant amount of chlorophyll (70%) in its chemical makeup. Given that it shares a structural resemblance with haemoglobin, it also results in a high oxygen supply to all tissues. Plant extracts with high levels of carotenoids and chlorophylls are especially crucial since they may exert a variety of protective effects through a number of pathways (7).

Although exploratory study on wheatgrass has been reported (8), there hasn't been any systematic or

extensive information published yet on the blood levels of total antioxidant capacity (TAC), catalase (CAT), and reduced glutathione (GSH) in ulcerated Wistar rats. With ethanolic extract made from dried wheatgrass shoots maintained under certain growing circumstances, the current study set out to assess the ethanol-induced alterations in biochemical and antioxidant indices in the colitis of Wistar rats.

MATERIALS AND METHODS

Plant material

To make wheatgrass, *Triticum aestivum* seeds (which were purchased from Ozone International in Mumbai and soaked the previous evening) were utilized. They were then lightly sprayed with water for a few hours and then indirectly exposed to sunlight. On the seventh day, Dr. Keshava Chandra K. of the Department of Botany at St. Agnes College in Mangalore, Karnataka, India, collected and certified the lab-controlled wheatgrass grass.

Preparation of wheatgrass extract

The young wheatgrass was newly collected, cleaned in distilled water after being washed with tap water, and then dried at room temperature (37 ºC) in the midday sun. The dried leaves were first ground into a fine powder in a spick and span electric blender in order to prepare the powder for extraction. Then, using a Soxhlet extractor and a weighed amount of wheatgrass powder, hot extraction was performed for 24 hours at 50 ºC. (9). Concentrating the acquired solvent extracts in a rotating vacuum evaporator at a temperature of 40 to 60 ºC until all solvent was eliminated, producing an extract sample. For the animal experiments, a 2% concentration of the isolated substance was dissolved in gum acacia.

Study animals

The study employed male wistar albino rats weighing 200-300g. They were obtained from Mangalore's institutional animal care centre, NUCARE. Each autoclaved polypropylene cage housed six rats. The cages were changed on a weekly basis. They were maintained at a temperature of 232 °C, with a relative humidity of 45 to 65% and a 12:12 dark/light cycle. Prior to treatment, the rats were given a seven-day acclimatization period. Animals were monitored daily for clinical symptoms throughout this time. With the exception of the overnight fasting prior to the induction of experimental ulceration, the animals were fed a regular mouse meal and filtered water as needed during the experimental phase. During this period, only filtered water was available to the animals. The K.S. Hegde Medical College in Mangalore's institutional animal ethics committee (IAEC) gave its approval to the experimental protocol (Reg. 115/1999/CPCSEA).

Experimental design

Eight groups made up a total of 48 rats (six rats in each group).
Group 1: For 7 days, 0.9% saline was administered orally to the control group once daily.
Group 2: Orally administered 1 ml/200g ethanol to animals with ulcers.
Group 3: Omeprazole (20 mg/kg) pre-treated animals with ethanol ulcers.
Group 4: Rats with ethanol ulcers who were then given omeprazole (20 mg/kg).
Group 5: Oral administration of 200 mg/kg BW of wheatgrass extract to rats with ethanol ulcers.
Group 6: Wheatgrass extract 200 mg/kg BW was given orally to rats with ethanol ulcers as a post-treatment.
Group 7: Oral administration of 400 mg/kg BW of wheatgrass extract to rats with ethanol ulcers.
Group 8: Wheatgrass extract 400 mg/kg BW was given orally to rats with ethanol ulcers as a post-treatment.

Using an oral tube suspended in 0.9% saline, omeprazole and wheatgrass were both given orally. On the fourth day, rats were fasted for 24 hours, and on the fifth day, rats received an oral injection of stomach ulcer medication (1 ml/200g). In order to separate the serum on the eighth day, blood samples were taken directly from the heart.

Collection of tissue sample, blood and gastric juice

One hour after ulcer induction, animals were slain by cervical dislocation after being anaesthetized for 2 to 5 minutes with a cotton ball saturated with 1.9% diethyl ether in a small chamber. The clear serum was obtained by drawing blood, centrifuging it for 10 minutes at 3000 rpm, and keeping it at 20 °C until analysis. Animal intestines were quickly extracted while also being split open along the larger curvature. Stomach tissue samples were meticulously cleansed with phosphate buffer saline (PBS) to eliminate any blood clots before being inspected macroscopically to determine the gastric ulcer index (4). Each stomach was then divided into two parts. Both components were homogenised at a ratio of 1:10 (w/v) in 0.1M potassium phosphate buffer, with one portion being placed in 10% formaldehyde for histological analysis. The homogenates were centrifuged using a 3-18KS Sigma cooling centrifuge from Germany at 3000 rpm for 10 minutes at 4°C. Myeloperoxidase (MPO) activity was present in the pellets that were produced, and the supernatants were stored at a low temperature for upcoming biochemical research.

Evaluation of gastric ulcer index

The ulcer index for each group was calculated using the formula below:

Ulcer index = Sum of lesion areas/Total stomach area x 100

The ulcer preventive index (%) was determined using the formula:

Preventive index = Ulcer index (ulcerated control)-Ulcer index (treated)/Ulcer index (ulcerated control) x 100

Biochemical analysis in tissue homogenate

Myeloperoxidase activity

The supernatant sample was mixed uniformly with a citric phosphate buffer solution containing 0.4 mg/mL O-phenylene diamine, 0.015% hydrogen peroxide, and a pH of 5.0. Spectrophotometric analysis was used to quantify the change in absorbance at 492 nm. use horseradish peroxidase to compare the reference dilution's absorbance to the test absorbance. Myeloperoxidase (MPO) was quantified in wet scrapings using (U/gm) units per gram (10).

Determination of MDA level

Melondialdehyde (MDA) levels in cell lysate were determined spectrophotometrically to evaluate lipid peroxidation, as described by Jose *et al.,* (2018) with slight modifications (11). Briefly, a reaction mixture containing 0.1 ml of the tissue sample, 0.2 ml of 8.1% sodium dodecyl sulfate, 1.5 ml of 2% acetic acid, and 1.5 ml of 0.8% aqueous solution of thiobarbituric acid. The pH of the solution was adjusted to 3.5 and the volume was finally made up to 4 ml with distilled water, followed by a 5 mL mixture of n-butanol and 15% pyridine was added. An ardent shaking was done to this combination. After 10 minutes of centrifugation at 4000 rpm, the organic layer's absorbance at 532 nm was calculated spectrophotometrically. Malondialdehyde (MDA) was expressed in units per gram (U/gm) of protein.

Determination of antioxidant indices

The total antioxidant capacity (TAC) was estimated by phosphomolybdenum (PM) assay using the standard procedure (12). Enzymatic assay like Catalase (CAT) activity test and non-enzymatic antioxidant assay, reduced glutathione (GSH), was determined by the method of Jose *et al.,* (11).

Histopathological examination

All groups had tissue samples collected mostly from the glandular region of the stomach, which was then fixed in 10% neutral buffer formalin overnight. According to Mousa *et al.,* routine tissue processing was done (13). Hematoxylin and eosin (H&E) staining was applied to tissue blocks that had been cut into 3-micrometer slices for histopathological analysis.

Statistical analysis

Six rats per group were used to calculate the mean and standard error of the mean (SEM) data, and One way ANOVA followed by Dunnett's test was used to identify statistically significant differences between groups. By using the GraphPad PRISM 5 software, the findings were statistically examined.

RESULTS

Ethanol-induced gastric ulcer

According to the results of this study, compared to the healthy control group, the experimental control group's stomach experienced gastric ulcers after receiving 1 ml of 90% ethanol orally. Animals in the group that were given ethanol extracts had their gastric ulcer response significantly decreased.

Effect of ethanol wheatgrass extracts on ulcer index, serum MPO, MDA, and gastric antioxidants

Rats with a high ulceration index were given oral doses of 90% ethanol, which caused gross lesions in the stomach lumen. An increased level of protection against ulceration was demonstrated by wheatgrass gavage prior to ethanol administration. Table 3 displays the considerable reduction in stomach ulcer index for both dosages of wheatgrass extract. More so than in the control group, the wheatgrass pre-treated group had an improvement in the stomach ulcer index. In comparison to the control group, the ethanol group's MPO activity were considerably higher. In contrast, MPO levels were significantly lower in the ulcerated group pre-treated with 200 and 400 mg/kg of extract than in the ethanol group. It's important to note that wheatgrass extract treatment groups showed more improvement in MPO activity than omeprazole-treated animal groups. Similar results were observed in gastric CAT, TAC, GSH, and MDA levels in ulcerated rats compared to normal groups. However, pre-treated wheatgrass extract at doses of 200 and 400 mg/kg observed substantial improvements in all antioxidant indicators, with values nearly as high as those observed in the ethanol group (Table 1).

Pathological findings on the gastric mucosa

Macroscopic findings

The gastrointestinal mucosa of the control rats was pale yellow, with a typical mucosal thickness (Fig. 1a). The ethanol-treated group severely displayed increased tissue responses, including severe dark red submucosal hemorrhagic strikes of various sizes accompanied by mucosal thickening (Fig. 1b). In the omeprazole-treated group the hemorrhagic vascular response decreased but the mucosa remained very congested and swollen (Fig. 1c).

The gastrointestinal mucosa of the treated rats revealed no harmful or degenerative effects in the groups pre-treated just with wheatgrass extract at both dosages, as normal, unclogged gastric mucosa with normal thickness was seen (Fig. 1d, 1e). Omeprazole post-treated GU showed less hemorrhagic streaks and no mucosal damage than the ulcer-control rats' GU did (Fig. 1f). Low mucosal damage is shown in the GU after treatment with 200 mg/kg BW of ethanolic wheatgrass extract, and reduced ulcer development is seen in the GU after treatment with 400 mg/kg BW of ethanolic wheatgrass extract (Fig. 1g and 1h).

Table 3: Biochemical parameters of gastric ulcer model and antioxidant levels

Groups	MDA (µM/L)	MPO (U/ml)	TAC (µg/mL)	Catalase (U/ml)	GSH (µg / protein)
Normal	5.91±0.56###	4.68±0.44###	0.57±0.10###	13.90 ± 0.93###	15.91±3.67###
Control (ethanol ulcerated rats)	15.73±2.29***	9.35±0.66***	2.28±0.75***	5.95 ± 0.22***	4.61± 0.55***
Standard drug- omeprazole pre-treated + ethanol ulcerated rats	5.64±0.51###	4.98±0.47###	0.56 ± 0.14###	12.32 ± 1.52###	17.81±1.37**###
Standard drug- omeprazole post-treated + ethanol ulcerated rats	3.91±0.34**###	4.43±0.71###	0.50 ±0.09###	13.76 ±1.38###	15.74 ±2.49###
Pre-treated with ethanolic extract of 200 mg/kg BW of wheatgrass + ethanol ulcerated rats	5.08±2.24###	5.89±0.42*###	1.46 ±0.03*#	12.64 ±1.05###	15.14±2.28###
Post-treated with ethanolic extract of 200 mg/kg BW of wheatgrass + ethanol ulcerated rats	4.45±0.60*###	5.79±0.50*###	1.56±0.03*	12.59± 0.78###	16.60±2.50###
Pre-treated with ethanolic extract of 400 mg/kg BW of wheatgrass + ethanol ulcerated rats	5.58±0.26###	5.75±0.89*###	1.66 ± 0.04*	13.24 ± 0.60###	17.47±1.38*###
Post-treated with ethanolic extract of 400 mg/kg BW of wheatgrass + ethanol ulcerated rats	4.15±1.03*###	4.85±0.57###	1.21 ± 0.09*#	12.98 ± 0.62###	16.77±1.63*###

Values are expressed as mean ± S.E.M (n=6) and analyzed by one-way ANOVA followed by Dunnett's test. *P < 0.05,**P < 0.01, ***P < 0.001 as compared to normal group; #P < 0.05, ##P < 0.01, ### p<0.001 as compared to ethanol control group.

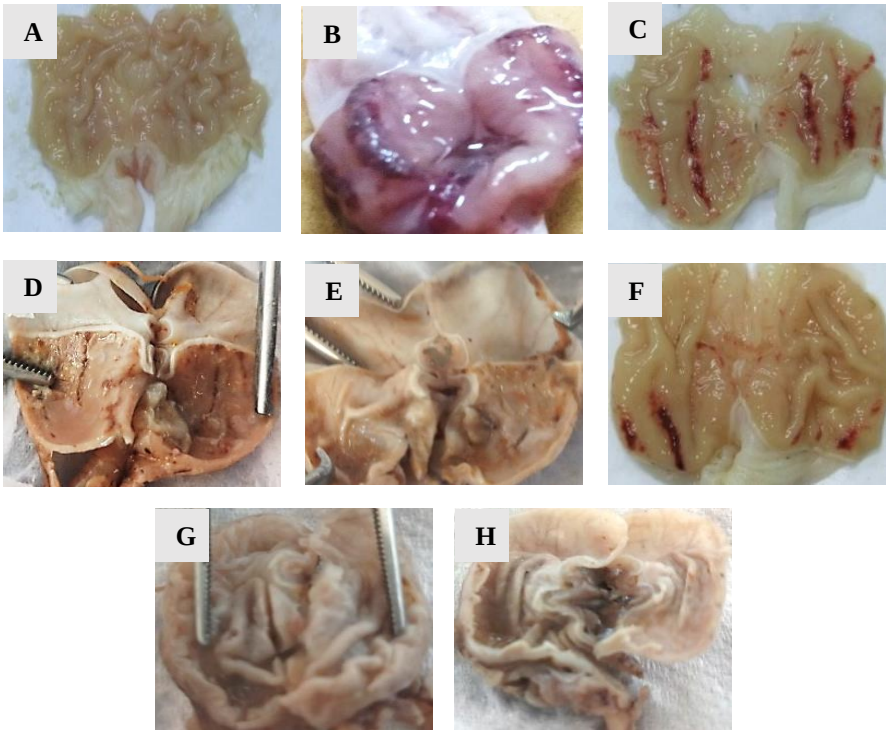

Fig. 1: Macroscopic appearance of the gastric mucosa of normal healthy stomach (control) rat (A); ethanol-induced gastric mucosal damage (GU) with severe mucosal injuries & extensive hemorrhagic streaks (B); GU pre-treated with standard drug-Omeprazole +Ethanol shows milder mucosal injury (C); pre-treated with 200 mg/kg BW the ethanolic extract of wheatgrass shows haemorrhage and ulcer spots (D); pre-treated with 400 mg/kg BW of ethanolic extract of wheatgrass and then induced ulcer with ethanol shows minimal mucosal damage compared to those of pre-treated with 200 mg/kg BW (E); omeprazole post-treated GU showing no mucosal injury & less hemorrhagic streaks compared to that seen in the ulcer control rats (F); GU post-treated with 200 mg/kg BW of ethanolic extract of wheatgrass shows low mucosal damage (G) GU post-treated with 400 mg/kg BW of ethanolic extract of wheatgrass with the less ulcer formation (H).

Histopathological examination of the colon

In control rats, there was no evidence of haemorrhages, congestion, or mucosal epithelium exfoliation, and the villi of the gastric mucosa remained intact (Fig. 2a). Multifocal edoema and mononuclear infiltration of inflammatory cells were present in the submucosal region in the ethanol-treated group. Furthermore, extensive inter-villus haemorrhages were linked to severe exfoliations in the mucous cells of the gastric mucosa (Fig. 2b). Other sections of the stomach mucosa showed extensive coagulative necrosis (Fig. 2c and 2d). The omeprazole-treated group showed that the extravasation of RBCs in the centre of gastric villi amid the intervillous gaps decreased significantly. Additionally, omeprazole medication has not significantly reduced the desquamation of the gastric mucosa's mucous cells or the full separation of the pyloric glands (Fig. 2e and 2f). The stomach tissue in the groups that received just wheatgrass extract at both dosages did not undergo any pathological alterations or deterioration; instead, the gastric mucosa reverted to being normal and intact, free from haemorrhages or congestion. no desquamation of the pyloric glands (Figs. 2g, 2h).

DISCUSSION

Alcohol intake has been identified as a significant factor in human gastric ulcer development. Thus, in order to evaluate the antiulcer efficacy of organic products or novel treatments intended to be utilized for gastric protection, researchers used the animal model of gastric damage triggered by ethanol to imitate circumstances to which people may be exposed (2). Due to its rapid and uncomplicated entry into the gastrointestinal mucosa, which results in gastric ulcers, 100% ethanol is harmful to stomach tissue in the animal model (14). These lesions may be identified by severe submucosal edoema, haemorrhage, desquamation of epithelial cells, and infiltration of inflammatory cells, all of which are signs of alcohol damage in humans (13). The goal of the current study was for the first time, compare the gastroprotective effectiveness of wheatgrass's aqueous ethanolic extract against ethanol-induced gastric ulcer to that of omeprazole, a commonly used and approved gastric ulcer treatment.

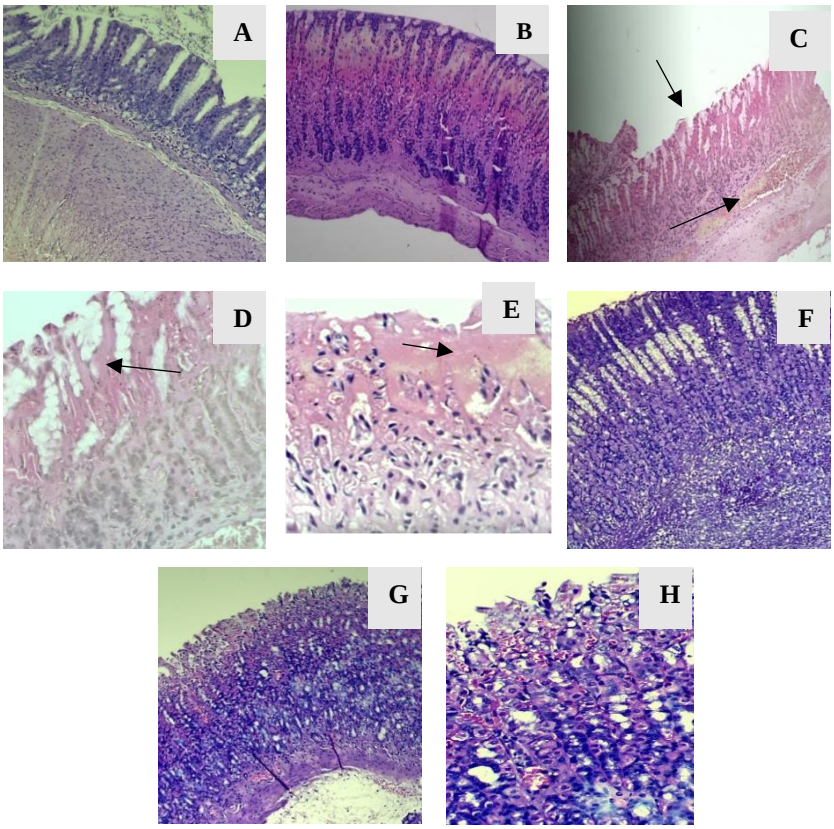

Fig. 2: Histopathological section of the gastric mucosa of normal healthy stomach (control) of rat (A); ethanol-induced gastric mucosa with (GU) with severe mucosal injuries & extensive hemorrhagic streaks (B); severe hemorrhage (arrow) with inflammatory cell infiltration & edema in the submucosal layer, arrow shows fibrin deposit in 10X (C) & hemorrhage in 40X (D); omeprazole pre-treated showing mild ulceration oedema and hemorrhage (arrow) in 40X. (E); omeprazole post-treated GU showing mild mucosal damage and reduced inflammation (F); GU post-treated with 200 mg/kg BW of ethanolic extract of wheatgrass shows ulceration, haemorrhage, and acute ulcer. (G) GU post-treated with 400 mg/kg BW of ethanolic extract of wheatgrass with less ulcer formation (H).

In the current investigation, rats treated with 100% ethanol developed severe ulceration. The evidence for this came from macroscopical and histological findings, which showed considerable bleeding as well as severe lamina propria submucosa congestion and inter-villus extravasation of RBCs inside the mucosal villi of the stomach tissue. These results might be explained by ethanol intoxication, which slows down the coagulopathy process and causes the haemorrhage to continue (15). Rats pre-treated with wheatgrass extracts showed a substantial decrease in the ulcer index at both doses when compared to the ulcerated group. Furthermore, ulcerated mice treated with wheatgrass had a greater reduction in ulcer index than the usual medicine omeprazole, showing that wheatgrass may be useful in the treatment of stomach ulcers. This finding is consistent with the findings of Abebaw *et al.,* (2017), who found that *Osyris quadripartite* Decne extract had a similar impact to a typical anti-ulcer medicine (16).

According to Kang *et al.,* (2014), one of the features of gastric ulcer is an inflammatory response, which encourages gastric mucosal damage by causing macrophages and leukocytes to migrate into the ulcer and its surrounding regions (17). During inflammation, migrating macrophages produce pro-inflammatory cytokines (18)-that promotes neutrophil infiltration in inflamed regions of the stomach and inhibits the gastric microcirculation surrounding ulcerated mucosa, delaying the healing of stomach ulcers (19,20).

Elevated gastric MPO activity generated by neutrophils is used to measure increased neutrophil infiltration into the stomach mucosa as a result of ethanol delivery (21, 22). In the current investigation, this was demonstrated by a significant rise in MPO activity in the stomach of rats treated with ethanol. The prevention of neutrophil infiltration into ulcerated gastric tissues is a crucial anti-inflammatory mechanism through which anti-ulcer drugs can expedite the healing of stomach ulcers and offer protection from them (23). As shown by the lowering of MPO activity, pre-treatment with wheatgrass extracts in ulcerated rats resulted in a substantial and dose-dependent decrease in neutrophil infiltration into the stomach mucosa, proving its anti-ulcer action.

Reactive oxygen species (ROS) produced by neutrophils in gastric mucosa play a crucial part in the gastric mucosal damage, according to Laine *et al.,* (24). Later, Kan *et al.,* (2017) demonstrated that ethanol-induced stomach ulcer pathogenesis and progression entail increased ROS generation and antioxidant depletion (25). The build-up of ROS causes lipid peroxidation as a result of their contact with the cell membrane, according to Yu *et al.,* (26). Similar to earlier studies by Sidahmed *et al.,* (2013), our findings showed that ethanol administration significantly reduced antioxidant enzyme activity levels (CAT, TAC, and GSH) and increased the concentration of MDA with concurrent depletion in GSH concentration in the ethanol group's gastric tissue (27). Contrarily, pre-treating ulcerated groups with wheatgrass extract had a significant protective effect against free radical-mediated oxidative damage by increasing the activity of antioxidant enzymes (CAT, TAC, and GSH), replenishing GSH levels that have been depleted, and lowering MDA levels. This antioxidant action of wheatgrass extract might be related to its high free radical scavenging activity, which is linked to the presence of a high concentration of potent antioxidants. This is in line with the findings of Mei *et al.,* (2012), who demonstrated that scavenging ROS is one of the processes behind ulcer healing (23). Our research demonstrated that wheatgrass extract has potent antioxidant properties equivalent to omeprazole. Previously, Ahmadi *et al.,* (2011) demonstrated that the therapeutic efficacy of a typical anti-ulcer medicine on ulcers might be connected to its antioxidant capacity via oxidative stress reduction mediated by hydroxyl radical scavenging (28).

CONCLUSION

When people are seeking rapid home remedies and turning their attention to traditional homoeopathic medicines with Vedic origins during the current pandemic crisis, wheatgrass may be a great option. The ability of wheatgrass to strengthen the immune system is possible. The findings of this study showed that the antioxidant and anti-inflammatory properties of wheatgrass extract in the aqueous ethanolic extract at both dosages prevented ethanol-induced gastric ulcers. The high concentration of phytoconstituents including total polyphenols, flavonoids, and tannins in wheatgrass extract may be the cause of its gastroprotective properties. The similar anti-ulcer impact of wheatgrass to that of omeprazole suggests that it may be employed as a potential anti-ulcer drug in the treatment of stomach ulcers. To further understand the underlying mechanisms of action, nevertheless, more study needs to be done.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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