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THERAPEUTIC IMPACT OF ALOE VERA GEL ON ETHANOL-INDUCED GASTRIC ULCER IN RAT THROUGH MODULATION OF MYD88 GENE EXPRESSION

Running title: Therapeutic Impact of Aloe Vera Gel on Ethanol-Induced Gastric Ulcer

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ABSTRACT

Gastric ulcers are among the major GIT problems impacting people globally. A number of natural compounds have been evaluated for gastric ulcer treatment. One of the most popularly used medicinal plants is Aloe vera, which has powerful anti-inflammatory and healing actions. Pantoprazole was used as a reference drug. The current investigation is intended to determine the therapeutic benefits of Aloe Vera in gastric ulcers triggered by ethanol in rats and to clarify if Aloe Vera achieves its therapeutic benefits by improving mucosal immunity through modulating MyD88 expression. Rats were divided into four groups: normal control, ethanol, ethanol + Aloe Vera, and ethanol + Pantoprazole. Gastric ulceration was triggered by giving only a single dose of 100% ethanol (5 ml/kg b.w.t.) orally. Aloe Vera and Pantoprazole were given orally for 2 weeks. At the end of the experiment, after rat sacrificing and stomach harvesting, macroscopic, molecular, and histopathological evaluations were done. The results revealed that the stomach mucosa in the ethanol group developed a severe ulcerative lesion. Also, myeloid differentiation primary response protein 88 (MYD88) gene expression was significantly upregulated. The ethanol group's histopathological examination revealed severe epithelial damage, inflammation, and edema. The macroscopic mucosal lesion, molecular alterations, and histopathological abnormalities are all alleviated by Aloe Vera treatment. Aloe Vera is more significant than medical treatment with pantoprazole. Finally, we concluded that Aloe Vera's ability to mitigate stomach ulcers is through its anti-inflammatory and healing capacities. Thus, Aloe Vera could potentially be utilized as a medication for relieving gastric ulcers.

Keywords: Aloe Vera, Ethanol, gastric ulcer, Rat, MYD88

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INTRODUCTION

Gastric ulcer is an ulcerative damage in the mucosal lining of the stomach that can extend to the submucosa and deep layers (Sreeja *et al.*, 2018). It is deemed to be one of the most dominant GIT disorders of the 21st century (Fahmy *et al.*, 2020). It affects almost 10% of the population worldwide, representing about four million people annually (Jabeen, 2018). Acute gastric ulcers typically result in severe gastric complications with a high death rate (Zhao *et al.*, 2020).

It is a complex and multi-causal disease. H. pylori infection and NSAIDs abuse are the most prevalent causes of gastric ulcers. Other risk factors implicated in gastric ulcers include stress, dietary habits, smoking, and alcohol consumption (El Badawy *et al.*, 2021). The basic underlying mechanism for stomach ulcers is an imbalance between destructive and protective factors in the gastric mucosa (Minaiyan *et al.*, 2021). The primary clinical sign is epigastric pain, which is often increased by eating. In severe cases, as in gastric bleeding, bloody vomiting and bloody stool occur. Other complications may occur, such as gastric perforation and obstruction, which may lead to death (Xie *et al.*, 2021).

Treatment of gastric ulcers mostly depends on acid suppression by conventional drugs such as proton pump inhibitors (PPIs) such as omeprazole and pantoprazole, histamine 2 (H2) receptor blockers such as ranitidine, and antacids. Prolonged use of these drugs has been reported to cause side effects. For instance, PPIs, the most commonly prescribed medications, cause osteoporosis-related fractures, pneumonia, arrhythmia, hematological abnormalities, and impotence and are also associated with the development of relapse (Yasin *et al.*, 2020). Moreover, H2 Blockers cause depression, dizziness, cardiovascular diseases, and thrombocytopenia (Chen *et al.*, 2022). Hence, there is a pressing need to develop novel anti-ulcer drugs of natural origin that are safe and have fewer side effects.

Medicinal plants have several immunopharmacological actions, which led to their use in drug discovery and industry (Kassem *et al.*, 2022). The WHO states that phytomedicines are crucial sources for the development of new drugs, and over 75% of people worldwide, particularly in developing nations, believe in and utilize herbal remedies for both the prevention and the therapy of various illnesses (Majumder *et al.*, 2019). Plants can be useful as a unique treatment approach for gastric ulcers due to their antisecretory, cytoprotective, and healing activities, which are the key characteristics of a gastroprotective substance that has a significant effect on the protection of stomach mucosa (Zakaria *et al.*, 2016). Aloe Vera is one of these plants that is being studied.

Aloe Vera originates from "Alloeh" (means "bitter and shiny substances") and "Vera" (means "true") (Sánchez *et al.*, 2020). It is a perennial succulent plant with a sticky and translucent gel with around 99% water and 1% solid contents, which contain about 75 active components such as vitamins, minerals, enzymes, hormones, carbohydrates, amino acids, sterols, and phenolic compounds. These ingredients have been reported to give the plant several biological activities (Embark and Abdalla, 2019). In preclinical and clinical studies, the therapeutic effects of Aloe Vera have been proven. (Svitina *et al.*, 2021). Along with the immunomodulatory, antioxidant, anti-inflammatory, cytoprotective, and curing activities of Aloe Vera stated in many studies, it might be utilized for gastric ulcer treatment (Zhu *et al.*, 2021).

The exact mechanisms of acute gastric ulcers are still largely unknown, but acute inflammation and inflammatory cytokines

are crucial in the damage of stomach mucosa and the occurrence of acute ulcers (Fu *et al.,* 2018). Previous research indicates that the TLR4/MyD88/NF-B classic inflammatory signaling pathway is the mechanism through which tissue injury induces a sterile inflammatory response. (Gao *et al.,* 2020). MyD88 is a key element in innate and adaptive immunity. It is a cytoplasmic protein that functions as an adaptor and signal transducer for most Toll-like receptors (TLRs) except for TLR3, connecting them to downstream molecules (El-Zayat *et al.,* 2019). It activates nuclear factor kappa B (NF-κB) to stimulate the transcription of inflammatory factors (Zakrzewska *et al.,* 2019). TLR4/MyD88/NF-κB is considered a classic inflammatory signaling pathway that is not only responsible for the transcription of inflammatory factors such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β and IL-6) but also inflammasome-related components contributing to the initiation of pyroptosis and the resultant massive inflammation (Lei *et al.,* 2018; Alavala *et al.,* 2019). Current research has reported that inflammasome and pyroptosis activation is a result of MYD88 activation (Wu *et al.,* 2021).

As MyD88 is a prerequisite for inflammatory signaling and inflammatory responses, its overstimulation and dysfunction lead to a wide range of inflammatory and autoimmune diseases with severe pathological consequences for the host (Zheng *et al.*, 2020)**.** According to previous research, activation of the TLR4/MyD88/NF-κB pathway is essential for the onset and progression of GIT disease (Lee et al., 2017). Thus, MyD88 appears to be a unique target for therapeutic intervention in gastric ulcers and other severe inflammatory diseases.

MATERIALS AND METHODS

1. Experimental animals:

Forty male Albino rats weighing about 180-200 grams were used in this study. Rats were supplied by the Faculty of Medicine's animal house, Assiut University. Before the study began, rats spent two weeks getting used to the laboratory environment. Animal handling and treatment were applied following the Animal House of Assiut University's rules, which were authorized by the Faculty of Medicine at Assiut University's ethical committee (IRP number 17300628).

2. Chemicals

Ethanol was obtained from Merck; Pantoprazole was obtained from El-Esraa Pharmaceuticals. Aloe Vera gel powder was purchased from Nature City (Florida, USA).

Experimental design:

Forty rats were distributed equally among these 4 groups (each group had 10 rats).

1. Normal control group: Rats drank distilled water for 2 weeks.

2. Ethanol group: Through gastric gavage, rats were administered one dose of 100% ethanol (5 ml/kg b.w.t.) after fasting for 24 hours (Eskander *et al.,* 2021).

3. Ethanol + Aloe Vera group: After 24 hours from gastric ulcer induction, rats were administered Aloe Vera gel powder dissolved in distilled water (200 mg/kg) once a day for 2 weeks by gastric gavage (Hassanshahi *et al.,* 2020).

4. Ethanol + Pantoprazole group: After 24 hours from gastric ulcer induction, rats were administered pantoprazole dissolved in distilled water (40mg/kg) once a day for 2 weeks by gastric gavage (Sahin *et al.,* 2019).

5. Finally, after sedation of rats with chloroform inhalation, they were killed by cervical dislocation.

3. Evaluation of stomach macroscopic picture

The stomach was opened at its greater curvature, lightly washed up with phosphate-buffered saline, and spread on filter paper for better evaluation of the ulcerative lesion.

4. Tissue samples:

After macroscopic evaluation, the stomach was split into 2 portions. One portion was immediately put in liquid nitrogen and kept at −80°C for qRT-PCR. The second portion was fixed in 10% buffered formalin for histopathological assessment. Each portion contains almost the same number of ulcers.

5. Quantitative real-time polymerase chain reaction (qRT- PCR).

The expression of mRNA was determined using qRT-PCR. Primers are listed in **Table 1**. RNA was isolated from gastric tissues using the RNeasy Mini Kit (catalog no. 74104, Qiagen, Germany) along with the supplier's directions. Reverse transcription of isolated RNA into cDNA was done by the High-Capacity cDNA Reverse Transcription Kit (catalog no. 4374966, Thermo-Fisher Scientific, USA) according to the supplier's directions. qRT-PCR amplification was carried out using the Maxima SYBR Green qPCR master mix (2x) kit (Catalogue No. #K0251, Thermo-Fisher Scientific, USA) and the 7500 Fast Real-time PCR machine (Applied Biosystems). The PCR cycling conditions were the initial denaturation at 95◦C for 10 min, followed by 40 cycles of 95◦C for 15 s and 60◦C for 60 s. β-actin served as a housekeeping gene. The relative expression was estimated from the $2^{-\Delta\Delta CT}$ formulation (Livak and Schmittgen, 2001).

Table 1: Primer sequences of rat MYD88 and β-actin genes.

Gene	Primer sequence
MYD88	**Forward:** 5′ CGACGCCTTCATCTGCTACTGC 3′
	Reverse: 5′ CCACCACCATGCGACGACAC 3′
β-actin	**Forward:** 5′ TGTCACCAACTGGGACGATA 3′
	Reverse: 5′ GGGGTGTTGAAGGTCTCAAA 3′

6. Histopathological examination

Each stomach sample underwent a process of fixation in a 10% buffered formalin solution, dehydration in increasing ethanol concentrations, clearing in xylene, and embedding in hard paraffin blocks. To determine histological alterations, 5µm thick tissue sections were stained with hematoxylin & eosin (H&E) (Abdelhady *et al.*, 2023).

7. Statistical analysis.

Data were described as means ± SD and analyzed using GraphPad Prism version 7 and a one-way analysis of variance (ANOVA) test followed by a least significant difference (LSD) multiple comparisons test. $P < 0.05$ was the significance level.

RESULTS

1. Effect of Aloe Vera on stomach gross picture

Gross evaluation of the gastric mucosa in the normal control group showed that the stomach was normal and intact **(Figure 1A).** On the contrary, the Ethanol-exposed group showed severe ulcerative damage **(Figure 1B).** In the ethanol + Aloe Vera group, it was found that Aloe Vera administration repaired the injured mucosa, as no obvious damage was found and just a slight congestion was seen **(Figure 1C).** The ethanol + pantoprazole group showed small ulcerative lesions **(Figure 1D).**

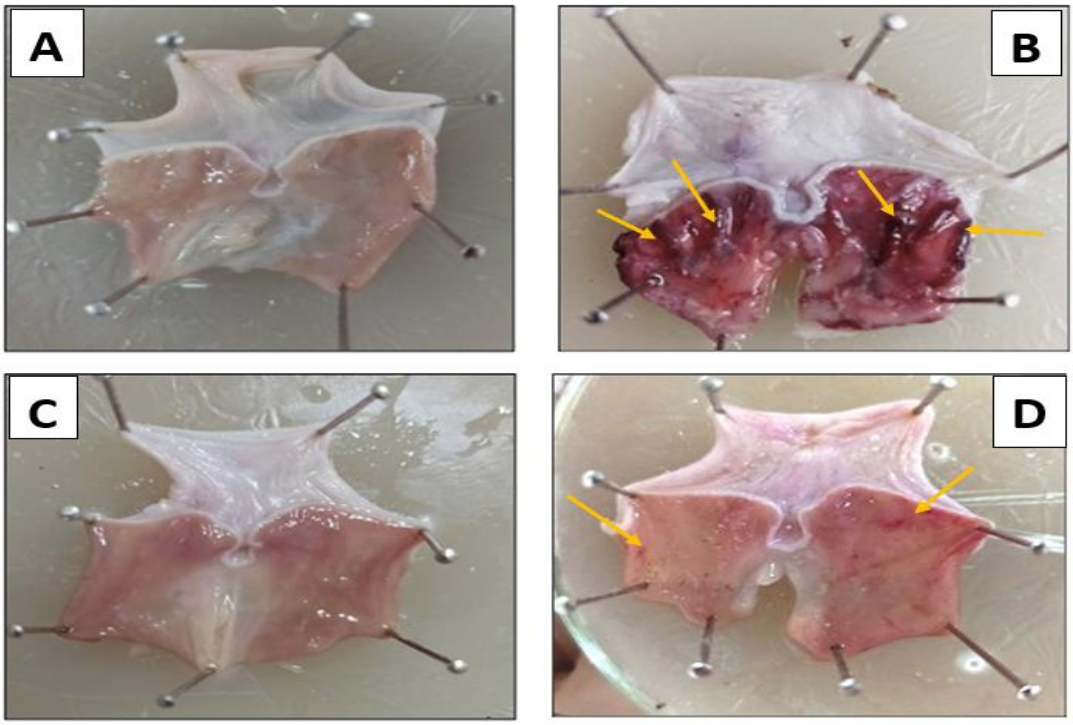

Figure (1): Gross evaluation of stomach in all experimental groups **(A)** normal control group; **(B)** Ethanol group; **(C)** Ethanol + Aloe Vera group, **(D)** Ethanol + pantoprazole group.

2. Effect of Aloe Vera on mRNA expression of MYD88

According to this study, the relative level of MYD88 mRNA expression was considerably greater in the ethanol group than in the normal control group (P<0.001). In contrast to the ethanol group, its expression level was considerably downregulated in the Ethanol+ Aloe Vera group (P<0.001) and Ethanol+ Pantoprazole group (P<0.001). Additionally, the Ethanol +Aloe Vera group's expression level was considerably lower than the ethanol +Pantoprazole group's (P=0.048) (Figure 2).

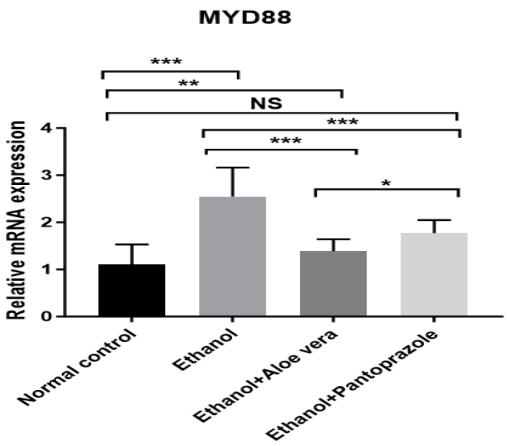

Figure (2): Relative mRNA expression of MYD88. Data were described as means ± SD.

Non-significant (N.S) **P** > 0.05 *P <0.05
**P < 0.01 *** P < 0.001

3. Effect of Aloe Vera on histopathological changes

(Figure 3A) showed H&E-stained sections from the stomach of the normal control group with the normal histological organization of the stomach, while **(Figure 3B)** showed the serious destructive action of ethanol on gastric structural integrity, which manifested as severe epithelial desquamation and mucosal necrotic and hemorrhagic lesion with submucosal oedema and inflammation. whereas the ethanol + Aloe Vera group showed histologically normal covering mucosa with slight submucosal infiltrations of inflammatory cells and oedema (**Figure 3C)**. The ethanol + Pantoprazole group showed considerable desquamation of epithelium, mucosal necrosis, and considerable infiltration of inflammatory cells and edema in the underlying submucosa **(Figure 3D).**

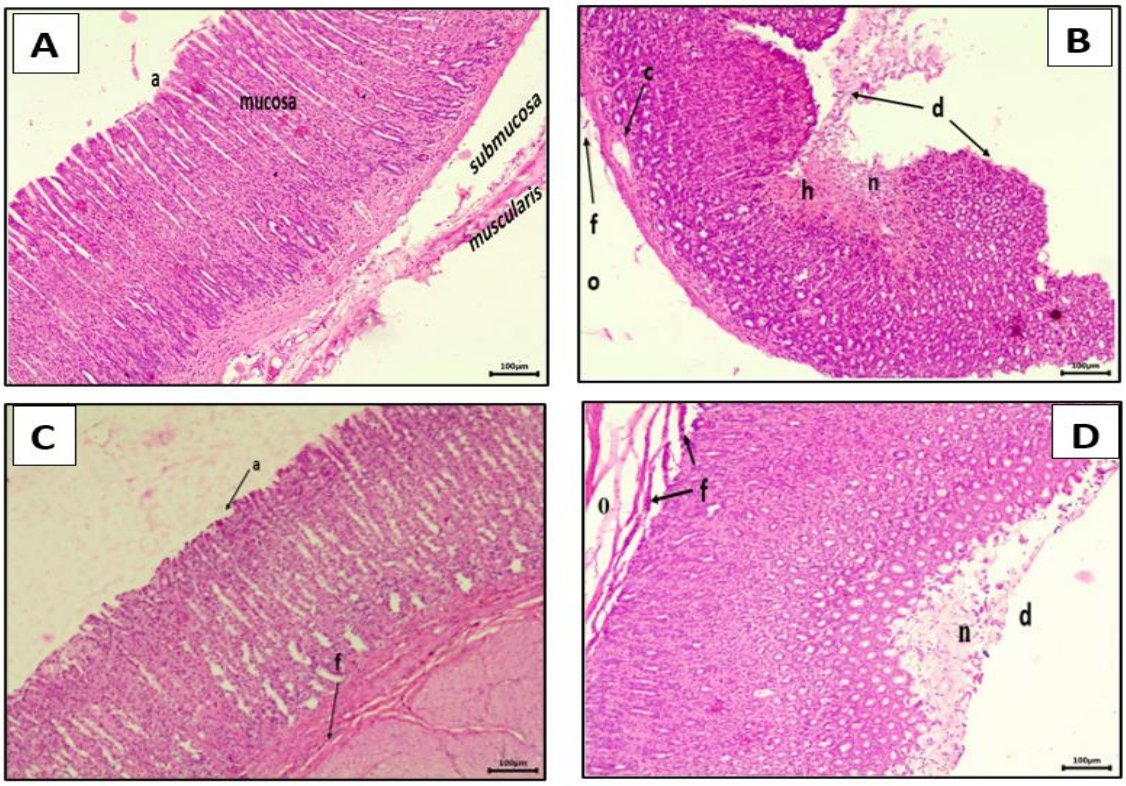

Figure (3): Histopathological alterations of the stomach in studied groups. H&E. (scale bar 100 µm). **(A) The normal control group** revealed that the stomach has normal histological organization. **(B) Ethanol group** showing (d) desquamation and detachment of epithelium in stomach lumen, mucosal (h) hemorrhage and (n) necrotic lesion with inflammatory cells infiltration, submucosal (c) congested BVs, (o) oedema with (f) inflammatory cells infiltration**. (C) Ethanol +Aloe Vera group** showing (a) intact epithelium, (f) slight submucosal inflammatory cell infiltrations. **(D) Ethanol+ Pantoprazole group** showing (d) considerable epithelium desquamation, (n) mucosal necrosis with considerable infiltration of inflammatory cells and submucosal (o) oedema and (f) inflammatory cell infiltration.

DISCUSSION

Gastric ulcer is among the most popular GIT ailments, disturbing more than 80% of underdeveloped nations and 40% of developed nations' populations (Abd el-Rady *et al.*, 2021). As the majority of synthetic pharmaceuticals used to treat gastric ulcers are overpriced and have undesirable effects, current medical research is focused on developing innovative, safe, and potent anti-ulcer therapies of natural origin. When compared to anti-ulcer drugs, plant extracts are more recommended because they have broad safe margins and minimal or no negative impacts on patients' health (Abo-Elsoud *et al.*, 2022).

Numerous studies have reported that Aloe Vera has antioxidant, anti-inflammatory, cytoprotective, and healing actions (Huseini *et al.,* 2015). In this regard, the objective of this study was to compare the possible therapeutic effects of Aloe Vera and pantoprazole on ethanol-induced gastric ulcers. Several scientific investigations on the anti-ulcer effects of Aloe Vera have been published. To the extent that we know, this is the first investigation to evaluate how Aloe Vera affects the expression of MYD88 in gastric ulcers.

The results of this research showed that Aloe Vera notably alleviated the ethanol-triggered (1) acute gastric damage (improved mucosal gross picture) and (2) inflammation (downregulated gastric MYD88 expression level). Additionally, the histopathological results confirmed our findings. Interestingly, the current investigation showed that Aloe Vera was more effective than pantoprazole at mitigating the effects of ethanol-evoked gastric ulcers.

In this study, an absolute ethanol-triggered gastric ulcer model was created. Absolute ethanol-evoked gastric ulcer is the most commonly used model for exploring the underlying pathophysiological mechanisms and the efficacy of natural ingredients as innovative antiulcer medications (Lebda *et al.,* 2018). In animal models, oral administration of absolute ethanol can directly destroy the protective mucosa, leading to acute gastric ulcers in one hour, which is typical of acute gastric ulcers in people (Ren *et al.*, 2021). Herein, oral ethanol administration caused severe and widespread ulceration in the stomach, which was seen macroscopically as severe hemorrhages. These results were supported by histopathological assessment, which showed severe epithelium destruction, local necrosis, and hemorrhage in the mucosa with vascular damage and inflammatory cells, as well as extensive oedema in the submucosa. In recent research, similar findings have been published by (Asaad and Mostafa, 2022 and Salaheldin *et al.*, 2023).

However, treatment with Aloe Vera greatly decreased gastric lesions and stimulated healing more effectively than pantoprazole since there were no signs of stomach ulcers in the ethanol + Aloe Vera group, while the ethanol + Pantoprazole group revealed some ulcerative damage. Through histological alterations, these results were verified. These outcomes concurred with previous research (Subramania *et al.,* 2006 and Jimmy *et al.,* 2020).

These results imply that Aloe Vera may have therapeutic and ulcer-healing properties. The healing effect of Aloe Vera may be due to the presence of active components such as auxin and gibberellin that help in the healing of wounds by acting as growth hormones for

stimulation of cell proliferation, regeneration, and growth. (Tiwari and Upadhayay, 2018). Aloe gel's ability to promote wound healing has been attributed to a number of mechanisms, including maintaining a moist wound, enhancing epithelial cell migration, and accelerating collagen maturation (Kumar *et al.*, 2019).

At the molecular level, we assessed the level of MyD88 expression in the gastric mucosa to determine if innate immunity was associated with the treatment of gastric ulcers. MyD88 is a universal adaptor downstream of most TLRs; it activates NF-κB to trigger the transcription of inflammatory cytokines, so it is considered the canonical adaptor for most inflammatory signaling pathways (Deguine and Barton, 2014). NF-κB is the primary transcription factor controlling inflammatory reactions in gastric cells. Proinflammatory substances produced by NF- κB create a powerful signal for controlling inflammatory immune cells implicated in inflammation (Lin *et al.*, 2017).

As soon as TLRs identify stimuli, a signal is transmitted from TLR4 to MyD88, which subsequently binds with Interleukin-1 receptor-associated kinase 4 (IRAK-4) to create the MyD88-IRAK-4 complex. As long as IRAK4 and TNF receptor-associated factor 6 (TRAF6) are continuously recruited, the IκB kinase (IKK) complex will be stimulated, resulting in the proteasome's destruction of Inhibitor of NF-κB (IκB). After that, the NF-κB p65 subunit is permitted to migrate to the nucleus and induce the transcription of proinflammatory factors (Tsubaki *et al.*, 2015).

In our study, oral administration of ethanol caused significant upregulation of MYD88 expression in the gastric mucosa of the ethanol group. In contrast, treatment with Aloe Vera reduced it to a near-normal level, suggesting that Aloe Vera exerted significant anti-inflammatory activity via downregulation of MYD88 expression, causing inhibition of the TLR4/MyD88/NF-κB signaling cascade, which subsequently attenuated inflammatory response.

These findings concurred with those reported by Fu *et al.* (2021), who found that ethanol up-regulated the expressions of MyD88 in gastric mucosa and that treatment with Periplaneta americana extract down-regulated MYD88 protein expressions, which alleviated ethanol-induced gastric ulcers. Also, our finding agreed with previous research that reported that inhibition of MYD88 expression improved gastric mucosal immunity and attenuated ulcerative damage in indomethacin-induced gastric ulcers (Song *et al.*, 2020) and ethanol-induced gastric ulcers (Fu *et al.*, 2022), indicating that MYD88 has a crucial role in the pathophysiology of gastric ulcer. In addition, Cui *et al.* (2014) found that Aloe Vera mitigated alcohol-induced hepatotoxicity and inflammation in mice via significant MyD88 downregulation. Also, Kim *et al.* (2015) showed that inhibition of proinflammatory cytokines was mediated by downregulation of MyD88 in an *H. pylori*-induced gastritis model.

Inhibition of Myd88 minimizes NF-κB activation and subsequent transcription of genes that control inflammation in gastric epithelial cells. In this respect, we can speculate that the therapeutic effect of Aloe Vera on gastric ulcers was achieved by inhibiting gastric inflammation through the downregulation of MYD88 and inhibition of the TLR4/MYD88/NF-κB signaling

pathway. So, Aloe Vera is thought to be a potent anti-inflammatory. These results may provide an innovative therapeutic approach for gastric ulcer therapy through modulation of MYD88 gene expression.

CONCLUSION

These findings concluded that treating rats with Aloe Vera could effectively treat the erosive effect of ethanol on the stomach and hasten the healing process of ulcers significantly more than pantoprazole. The therapeutic outcome of Aloe Vera is attributed to its anti-inflammatory and healing effects. Furthermore, we demonstrated for the first time that the therapeutic impacts of Aloe Vera on gastric ulcers are strongly mediated by suppression of MyD88. These findings provide a different concept to explain the use of Aloe Vera as a natural medicinal agent in clinical settings for the treatment of gastric ulcers.

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التأثير العلاجى لجل الصبار على قرحة المعدة التى يسببها الإيثانول فى الجرذان من خلال تعديل التعبيرالجيني لجين MYD88

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تم تصميم هذه الدراسة لتقييم التأثير العلاجى لجل الصبار على قرحة المعدة التى يسببها الإيثانول فى الجرذان وذلك عن طريق الفحص العينى والمجهرى للمعدة وايضا قياس التعبير الجينى لجين MYD88. أجريت هذه الدراسة على 40 من ذكور الجرذان البيضاء تم توزيعهم على أربع مجموعات كل مجموعة تحتوى على 10 جرذان (مجموعة ضابطة ، مجموعة الإيثانول ، مجموعة معالجة بجل الصبار، مجموعة معالجة بالبانتوبرازول). تلقت المجموعة الضابطة ماء مقطر لمدة اسبوعين. أما مجموعة القرحة تم اعطائها جرعة واحدة من الإيثانول المطلق عن طريق الفم (5مل / كجم) بعد 24 ساعة من الصيام ثم تم التضحية بهم بعد ساعة واحدة من اعطائهم الايثانول. بينما المجموعة المعالجة بجل الصبار تم إعطائها جل الصبار بجرعة (200مجم/كجم/يوم) عن طريق الفم لمدة أسبوعين بعد إحداث القرحة. أما المجموعة المعالجة بالبانتوبرازول تم اعطاء الجرذان بانتوبرازول عن طريق الفم بجرعة (40 ملجم / كجم / يوم) لمدة اسبوعين بعد إحداث القرحة. استغرقت الدراسة أسبوعين. خلصت نتائج هذه الدراسة الى تفوق جل الصبارعلى البانتوبرازول فى علاج القرحة حيث ان العلاج بالصبار والبانتوبرازول أدى الى انخفاض معنوى فى مستوى تعبيرجين MYD88 مقارنة بمجموعة القرحة ولكن عند المقارنة بين البانتوبرازول والصبار نجد أن الصبار قد أدى الى انخفاض معنويا فى MYD88 مقارنة بالبانتوبرازول. أظهرالفحص العينى والمجهرى ان التغيرات التى سببها الايثانول فى مجموعة القرحة مازالت موجودة ولكن بدرجة اقل فى المجموعة التى تم علاجها بالبانتوبرازول بينما وجد ان المجموعة التى تم علاجها بالصبار مشابهه الى حد كبير للمجموعة الضابطة.