PROTECTIVE ROLE OF ALHAGI GRAECORUM BOISS ON INTESTINAL FUNCTION AGAINST ASPIRIN IN ADULT MALE RABBITS

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Abstract

The effect of *Alhagi graecorum* Boiss on intestinal function and morphological changes in response to aspirin-induced intestinal damage was investigated in this study on male rabbits. The experiment employed twenty healthy adult male rabbits. The animals were separated into four groups. at random (5 rabbits per group) and treated for 42 days as the following: a control group (C): Rabbits were allowed free access to drinking water, T1 group: Animals received (10 mg /kg b.w) of aspirin orally , T2 group: were administered 400 mg/ kg b.w ethanolic extract of *Alhagi graecorum* and 10 mg/kg of aspirin orally , T3 group: animals were given 400 mg/ kg b.w alcoholic extract of *Alhagi graecorum* orally. After 42 days of the experiment, D-xylose absorption test was performed for all animals. Blood samples and intestinal segments were collected at the end of the experiment. The results shown that oral intubation of Aspirin for 42 days caused intestinal dysfunction manifested by a substantial decrease ($P<0.05$) in D-xylose in the T1group, whereas the animals given *Alhagi graecorum* showed a considerable elevation ($P<0.05$) in the levels of D-xylose. The histomorphological examination revealed significant reduction($P<0.05$) in goblet cells size and density, villi high, villi thickness, enterocyte and crypt depth in T1 group compared to other groups while all these parameters considerably increased ($P<0.05$) in animals received *Alhagi graecorum*. Furthermore animals received aspirin had significant ($P<0.05$) reduction in food intake and body weight whereas animal received *alhagi graecorum* exhibited substantial ($P<0.05$) increase in both food intake and body weight. It can be concluded that intestinal deleterious changes induced by aspirin can be prevented by *Alhagi graecorum* extract.

Keywords: D-xylose, Histomorphology , food intake , body weight.

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reduced aspirin side effects on gastric mucosal damage. (Zhu *et al*., 2021) Therefore, it is critical to find other medications that reduce gastrointestinal injury caused by aspirin mucosal damage. As a result, the current experiment was designed to find a strategy to reduce aspirin-induced gastrointestinal injury.

2. Materials and method

Preparation of plant extracts

Alhagi graecorum plant was collected in March 2022 from the river area southern Baghdad city, Iraq. The plant samples were cleaned, shade-dried, crushed and for each 50 gm mixed with ethanol 98% kept in shaker at (35c˚) for (72 hr.) and then thoroughly filtered via different size filters, then placed in incubator for about 3 days The filtrate was concentrated (approximately 10 g / 100 g crushed plant) and used to make a diluent by normal saline.

Experimental design

Twenty healthy adult male rabbits, weighted (1500- 1750 g) were divided into four equal groups at random.: control group (C): The rabbits in this group were given unlimited access to drinking water., T1 group: Animals received (10 mg /kg b.w) of aspirin orally , T2 group: were administered 400 mg/ kg b.w alcoholic extract of *Alhagi graecorum* and 10 mg/kg of aspirin orally , T3 group: Orally administered 400 mg/kg b.w. alcoholic extract of *Alhagi graecorum*, for 42 days. At the end of experiment rabbits were anesthetized, sacrificed via drag the blood from the heart, after that small intestine was excised, opened longitudinally, washed with normal saline and conserved in 10% neutral buffered formalin for 10 days, then prepared for paraffin embedding technique and partitioned at 6 µm with rotary microtome, after that stained with hematoxylin and eosin stain.

Intestinal histomorphological measurements (villi Height, Thickness of villi, crypt depth, goblet cell density and size)

The histomorphological measurements were measured per each segment of intestine,10 fields/ animal of 3 animals/group,30 fields for each group at 40X to measure; Villus Height (µm), Villus thickness (µm), crypt depth (µm), HV/CD, Goblet size (μm^2) and Goblet density (cell/100 µm). The tissue sections were examined by light microscopy and microphotography has been done by using

1. Introduction

Medical plants have been used to relieve pain and treat diseases in all parts of the world since ancient times in folk medicine. Medicinal plants also have stimulating effects on digestive system of animals (Sulaiman and Tayeb, 2021). One of these plants is *Alhagi graecorum*, which has been widely used for a variety of medicinal purposes. *Alhagi graecorum* a species of genus Alhagi (Fabaceae) in Iraq, locally called Aqual. It is rich in phenolic compounds, flavonoid, anthraquinone, glycosides, steroids, saponins, alkaloids and tannins (Mohammed and Abd-alkadhemand, 2022). It is a perennial plant with a wide geographic range. Its effects have been studied in both animal and human studies, and some of them include antioxidant, antipyretic, anti-inflammatory, diuretic, diaphoretic, expectorant, analgesic and anticancer properties. (Srivastava *et al*.,2014; Al-Snafi, 2015). Flavonoids are secondary metabolites that have anti-allergic, anti-inflammatory, antibacterial, antiviral, and antifungal properties. (Loizzo *et al*.,2014; Hamad and Alwash, 2021). Aspirin is one of the oldest medications still widely used today, with a long history of antipyretic, analgesic, and anti-inflammatory properties. (Zhang *et al*., 2020; Waheb and Mohammed.2022). Aspirin is among the most widely used medications in the world. due to its antiplatelet activity in the prevention and treatment of thrombosis (Alegbeleye, 2020) . Regardless of its therapeutic uses, aspirin has been related to gastrointestinal (GI) toxicity, which ranges from acute mucosal damage to GI problems and death. (Huang *et al*.,2010; Lavie *et al*.,2017). The most common adverse effect of aspirin is gastrointestinal upset, which can vary from gastrointestinal bleeding to gastritis. (Weltermann and Macke, 2021) in addition to gastric ulcer (Al-Shaha& Mohammed, 2017). Even when aspirin coated still from 10 to 25% of aspirin users may develop peptic ulcer (Guthrie, 2011) attributed to gastrointestinal bleeding (Chen *et al*., 2017). Aspirin mechanism in damaging gastrointestinal mucosa mediated by damaging mucus layer of the intestinal mucosa (Zhu *et al*., 2018). It was discovered that proton pump inhibitors (PPI), which are used to prevent gastric mucosa, cause damage to the phospholipid layer of the intestinal mucosa. (Wallace, 2012). By reducing platelets aspirin activating process, Xuesaitong and aspirin combination effectively

Food intake (gm)

Was recorded daily during the whole experimental period for each cage (7 animals)/ day, by abstraction of remaining food from given amount (Vento *et al*., 2008) for day zero. For the 20th and 42th the food intake average estimated for 20 days, and 22days respectively.

Statistical analysis

Data is presented as the Mean± SE. Within the SPSS program, data was analyzed using two-way analysis. LSD was used to test the means at a probability level of ($p<0.05$).

3. Results

Results of the effect of oral intubation of aspirin and *Alhagi graecorum* on food intake during different experiment period are exhibited in table 1. At zero time of the experiment the food intake showed no substantial ($P >0.05$) differences among T1, T2 and T3 groups (688.00±19.84), (686.00±20.63) , (689.00±23.89) in compared to control group (690.00±29.15). After 20 and 42 days of experiment T3 exhibited significant ($P<0.05$) raise in food intake (750.00±15.81), (915.00±15.00) in associated to other groups whereas T1 group displayed statistical ($P<0.05$) reduction (610.00±33.16) compared to other groups within the same period of experiment and continues to the end of experiment period (360.00±18.70).

Future Win Joe microscopic camera, the images have been analyzed and scored by using Fiji image analyzer system. Villus Height (VH) measured as the distance between the tip of the villus to the crypt-villus junction and crypt depth (CD) was measured from villus base to the crypt- villus transition region, villi thickness is the mean of 3 readings; the top, middle and base of villi as reported by. For goblet cell size the longitudinal × transfers axis.

Absorption test (**D-xylose test**)

The technique of D-xylose absorption test:

The test is carried out on three rabbits from each experimental group. Before testing, rabbits are fasted overnight. D-Xylose solution (0.5 g/ kg/ b.w) (Guijarro *et al*., 2007) is administrated via stomach tube. Blood sample are taken at 1st, 3rd and 5th hour after administration. The spectrophotometric method described by (Eberts, 1079) was used to measure the amount of D-xylose in each serum sample. In short, 200 µL of serum was added to the 1000 µL of chromogen phloroglucinol, chloridric acid and acetic acid, after mixing boil in a water bath at 100 C˚ for 8 min. Then, in an ice bath, cool to room temperature. A spectrophotometer was used to measure optical density at 554 nm.

Growth performances

Body weight (gm)

It recorded at zero time, 20 and after 42 days of the experiment for each animal, using electron balance.

Table 1. Effect of oral administration of Aspirin and *A. graecorum* alcoholic extract on food intake for each animal (g/cage/day) at zero, 20 and 42 days of experiment.

Time / Groups	Zero time	20 days	42 days
C	690.00±29.15 Aa	698.00±23.53 Aab	725.00±15.81 Ab
T1	688.00±19.84 Aa	610.00±33.16 Ac	360.00±18.70 Bc
T2	686.00±20.63 Aa	640.00±29.15 Abc	695.00±16.58 Ab
T3	689.00±23.89 Ba	750.00±15.81 Ba	915.00±15.00 Aa
LSD	64.08		

Means with different small letters (columns) and capital letters (row) are significantly different ($P<0.05$). C: control group, T1: 10 mg /kg b.w of aspirin , T2: 400 mg/ kg b.w alcoholic extract of *Alhagi graecorum* and 10 mg/kg of aspirin,T3: 400 mg/ kg b.w alcoholic extract of *Alhagi graecorum*.

Results of body weight at different period of experiment represented in Table 2. Within same groups, the control, T1, T2 and T3 groups revealed no statistical changes (P >0.05) at zero time and after 20 days whereas after 42 days of the experiment time T1 exhibited significant reduction (P<0.05) in body weight (1020.00±51.47) in compared to control, T2 and T3 groups (1560.00±18.70), (1520.00±37.41) , (1730.00±20.00), while at the same period T3 presented statistical rise (P<0.05) in body weight (1730.00±20.00) in related to other experimental groups. On the other hand the result indicated that T1 group revealed significant drop (P<0.05) in body weight (1020.00±51.47) after 42 days of experiment time in compared to zero time and after 20 days (1540.00±24.49) , (1500.00±31.62). While during the same period T3 group showed statistical elevation (P<0.05) in body weight (1730.00±20.00) compared to zero and 20 days of the same group (1520.00±33.91), (1590.00±33.16).

Table 2. Effect of oral administration of Aspirin and *A. graecorum* alcoholic extract on the Body weight at zero**,** 20 and 24 days.

Time / Groups	Zero time	20 days	42 days
C	1550.00±59.16 Aa	1570.00±48.89 Aa	1560.00±18.70 Ab
T1	1540.00±24.49 Aa	1500.00±31.62 Aa	1020.00±51.47 Bc
T2	1530.00±60.41 Aa	1510.00±62.04 Aa	1520.00±37.41 Ab
T3	1520.00±33.91 Ba	1590.00±33.16 Ba	1730.00±20.00 Aa
LSD	121.89		

Means with different small letters (columns) and capital letters (row) are significantly different (P<0.05). C: control group, T1: 10 mg /kg b.w of aspirin , T2: 400 mg/ kg b.w alcoholic extract of *Alhagi graecorum* and 10 mg/kg of aspirin,T3: 400 mg/ kg b.w alcoholic extract of *Alhagi graecorum*.

Figure 1. represents the results of the serum D-xylose concentration during five hours interval of administration. During the 1st hour of D-xylose administration the serum concentration increased significantly (P<0.05) in control, T2 and T3 groups (0.45±0.04), (0.44±0.07), (0.53±0.03) in compared to T1 group which showed significant reduction (P<0.05) in the serum D-xylose concentration (0.27±0.02). The serum concentration of D-xylose continuously increased significantly (P<0.05) at 3rd hour in control, T2 and T3 respectively (0.49±0.003), (0.46±0.06) , (0.58±0.05) compared to T1 group which showed significant drop (P<0.05) in serum concentration (0.29±0.05). Whereas at 5th hour the serum concentration decreased significantly (P<0.05) in all groups of the experiment (control, T1, T2 and T3) (0.37±0.12), (0.26±0.04) (0.37±0.02) ,(0.36±0.03).

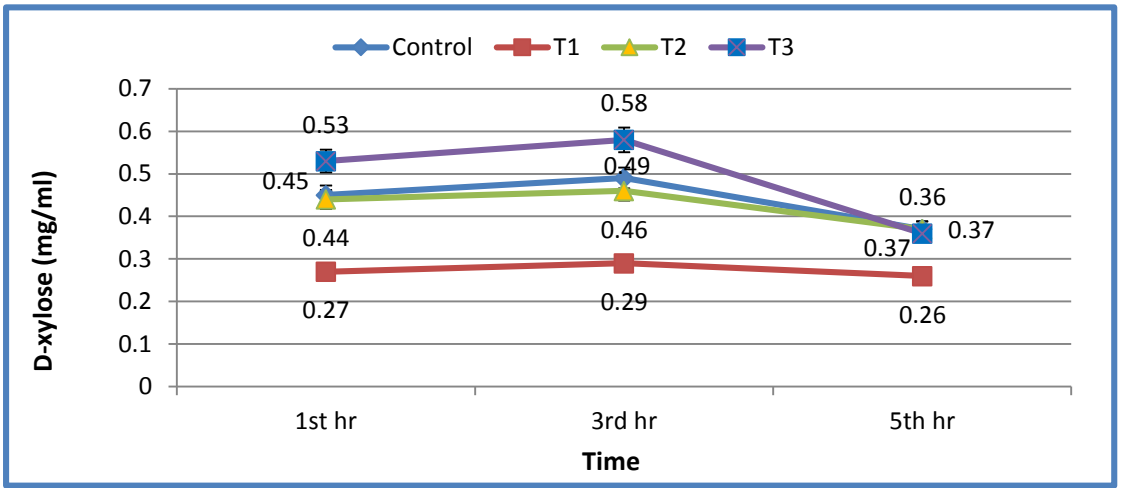

Figure 1. Effect of oral administration of Aspirin and *A. graecorum* alcoholic extract on the D-xylose test during 1st, 3rd and 5th hrs. (mg/ml), n=3, LSD= 0.16

The histomorphological changes of duodenum, Jejunum and ileum are illustrated in Table 9, 10 and 11. Which showed significant reduction ($P<0.05$) in villi high, thickness of villi, crypt depth, Goblet size and Goblet density in aspirin group compared to control, T2 and T3 groups, while in contrast all these histomorphological parameters significantly($P<0.05$) increased in T3 group in compared to other groups in all intestinal segments.

Table 3. Effect of oral administration of Aspirin and A. graecorum alcoholic extract on the histomorphological examination of duodenum.

Parameters / Groups	Villi height (µm)	Thickness of villi (µm)	Crypt depth (µm)	VH:CD	Goblet size (μm^2)
Control	244.08±4.75 b	43.87±3.67 c	68.19±2.67 b	3.59±0.13 ab	9.96±5.60 b
T1	172.50±4.98 c	34.80±0.84 d	54.28±2.19 c	3.18±0.09 b	13.79±8.74 a
T2	249.84±11.51 b	81.30±1.91 A	62.73±4.61 b c	4.09±0.42 a	11.64±11.60 ab
T3	299.28±4.75 a	70.02±4.01 b	81.14±5.14 a	3.75±0.25 ab	10.72±19.03 ab
LSD	21.33	8.74	11.58	0.78	3.68

Means with different small letters (columns) are significantly different ($P<0.05$). C: control group, T1: 10 mg /kg b.w of aspirin , T2: 400 mg/ kg b.w alcoholic extract of *Alhagi graecorum* and 10 mg/kg of aspirin,T3: 400 mg/ kg b.w alcoholic extract of *Alhagi graecorum*

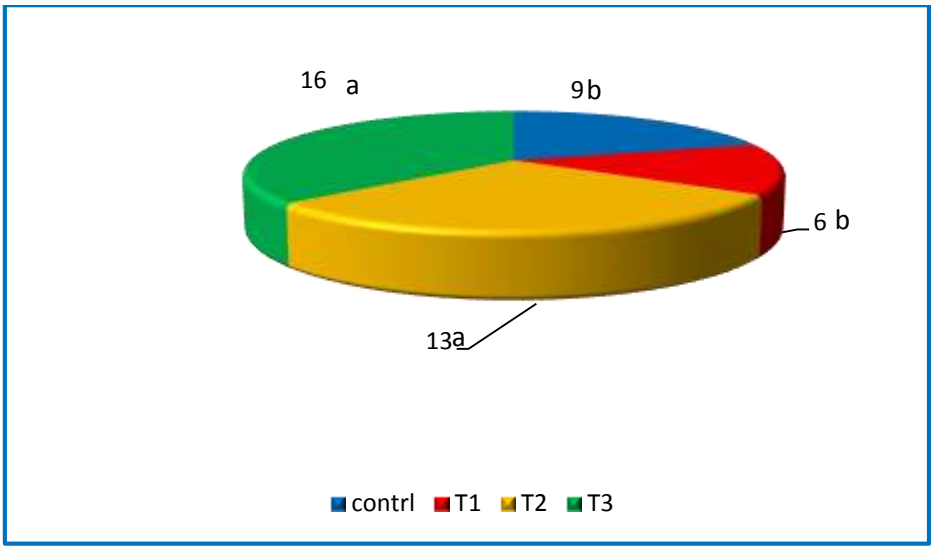

Figure 4-6. Effect of oral administration of Aspirin and *Alhagi. graecorum* alcoholic extract on goblet cells density(Cell/100 µm) of duodenum. LSD= 3

gut barrier function via following mechanisms: upregulation of glucagon-like peptide (GLP)-2 which might improve the function of the intestinal barrier (Oteiza *et al*., 2018; Del Bo *et al*., 2019) and maintenance of the intestinal tight junction barrier and structure (Hu *et al*., 2019). Additionally improving gut microbiota and their metabolites, which are associated with their anti-oxidative and anti-inflammatory functions (Navarre and Hellmann, 2022).

Inflammatory reactions of the intestinal mucosa mediated by cyclooxygenases (COX), both Cox-1 & COX-2, whose activation is involved in ischemia tissue injury of many organs, including the intestine (Khan *et al*., 2022). Inducible COX-2 activity has been associated with a number of inflammatory diseases such as inflammatory bowel. Aspirin is less effective in inhibiting COX-2 activity, additionally it Acetylation of Ser530 in COX-2 not only results in the formation of 15R-HETE, but it also enables for the oxygenation and cyclization of arachidonic acid into 15R-PG endoperoxide. 15R-PGs are novel products of aspirin treatment through acetylation of COX-2 and may related to its pharmacologic properties particularly antiplatelet effect (Fakree and Ali 2009.; Giménez-Bastida *et al*., 2019). The intestinal epithelium's primary functions are to regulate solute and fluid exchange in addition to absorb nutrients. (Odenwald and Turner, 2013). D-xylose absorption is a clinical laboratory test used to assess intestinal absorption. (Craig and tkinson ,1988). The absorption of the monosaccharide D-xylose does not require enzymes for digestion but only an intact mucosa. As a result, D-xylose absorption has been

4. Discussion

The denoted reduction in both food intake and body weight in aspirin insulted intestine after 42 days of the experiment. These finding are in agreement with the results obtained by **(**Al – Timimi,2020**)**, this demonstrated the deleterious effects of aspirin on the intestinal barrier. Aspirin found to reduce food intake in different ways one of them by alter intestinal barrier consequently reduced nutrient absorption. Furthermore, the symbiotic alteration causes an increase in pathogenic lipopolysaccharide transmission to circulation, which stimulates the secretion of Glucagon like peptide-1 (GLP-1) from EECs (Lebrun *et al*., 2017) which reduces food intake by affecting brain areas regulating appetite, (van Bloemendaal *et al*., 2014; Regnier *et al*., 2021). On the other hand PGs have been shown to be important in skeletal muscle myogenesis (Korotkova and Lundberg, 2014). Also, PGF2a stimulates muscle protein synthesis (Markworth and Cameron-Smith, 2011), loss of PG synthesis expected in the present experiment as a response to aspirin could be one of the mechanisms of reducing food intake and body weight. Whereas food intake and body weight decreased by aspirin, they were increase in the animals received *alhagi graecorum*. The use of medical plants as feed additives, which comprise a wide variety of herbs, has recently gained increasing interest potential alternative natural growth promoters (Beski *et al*., 2021). the polyphenols and other antioxidants content of *alhagi graecorum* can exert beneficial effects on gut epithelium through improving

hypoplasia. All of these changes indicate to the mucosal damage. Similar changes were found in rats had acetylsalicylic acid, the active gradient of the aspirin (Taslidere *et al*., 2018).In addition the histomorphological results showed that aspirin caused decrease in the Goblet cells size and density as well as reduction in villi high, villi thickness, and crypt depth. Because PGs play an important role in gastrointestinal epithelial preservation by increasing mucosal blood flow, a decrease in PG synthesis can result in intestinal mucosal damage. (García Rodríguez *et al*., 2016). MUC2 is a main constituent of the gel-like secreted mucus layer that coats the epithelium of small intestine and is expressed by goblet cells (Ambort *et al*., 2012, Bergstrom and Xia, 2013). This mucus layer affiliated with mucosal permeability and is critical to the function of the intestinal barrier. As a result of goblet cell dysfunction, mucosal permeability may increase, which can result in bacterial invasion or immune system dysfunction associated with a numerous intestinal diseases. Whereas the *Alhagi graecorum* administered groups showed an increase in villi height, which was associated with an increase in thickness of intestinal mucosa , this result suggests that, the effect of the *Alhagi graecorum* was very important to increase the secretory activities of epithelial cells and epithelial crypts, in addition to increase the population of these crypts, also there were increase of cellular population associated with hyper-cellularity and vascularization of connective tissue within lamina propria of villi which were clearly obvious those lead to increase both the thickness and height of villi consequently, this effect may be due to the potencial antioxidant constituent of *alhagi graecorum* particularly flavonoids and tannins (Al-Okaily *et al*., 2012 ;Dakheel *et al*., 2021).

5. Conclusion

In conclusion, our research discovered that taking *Alhagi graecorum* orally reduces aspirin-induced intestinal damage. antioxidative and anti-inflammatory properties of *Alhagi graecorum* may related to its protective effect. Accordingly, *Alhagi graecorum* may be a promising therapy for preventing aspirin-induced intestinal damage.

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recognized as an important functional indicator of small intestinal malabsorption. Aspirin damaged the small intestine mucosa, which reduced D-xylose absorption. The majority of NSAIDs, including aspirin, inhibit COX which catalyzes prostaglandin (PG) synthesis from arachidonic acid (Vane, 1971). Various mucosal functions such as increasing mucus secretion and mucosal tight junction (TJ) barrier in addition to Small intestinal blood flow are regulated by PG. The suppression of PG formation caused by NSAIDs leads to severe mucosal injury. TJs act as an intercellular gate or seal since they are placed on the most apical side of intercellular junctions. (Anderson and Van Itallie, 2009;Al-Sadi *et al*.,2011,). The COX-independent pathway, on the other hand, was suggested a three hypothesis: NSAIDs initially cause direct mitochondrial damage in the small intestinal epithelial cells. Then mitochondrial damage causes depletion of intracellular energy and free radicals production, which disrupts the intercellular junctions of the small intestinal epithelium. Finally, damaged mucosal TJ barriers allow intestinal bacteria, or toxins and bile acid to easily penetrate, causing mucosal damage. (Bjarnason *et al*., 2018). On the other hand the absorbance rate of D-xylose increased in animal received alcoholic extract of *Alhagi graecorum* at 1st hour and continue to increase at 3rd hour, possibly due to its content of tannins that may cause increased in villus perimeter, villus height and mucosal thickness. The intestinal villi's size is crucial for nutritional digestion and absorption capacity. (Zhang *et al*., 2013; Chen *et al*., 2021) as longer villi have a larger surface area for absorption (Han *et al*., 2014). Furthermore, flavonoid found in the plant which has antioxidant effect (Mashi, 2016) is believed to be essential in the protection of the intestinal epithelial barrier (Vezza *et al*., 2016). While at 5th hour the rate of D-xylose absorption decreased in all experimental groups because 60% of this sugar is excreted via kidney. The histomorphological changes of duodenum illustrated in Table 3. Which showed significant reduction ($P<0.05$) in villi high, crypt depth, thickness of villi, enterocyte, Goblet size and Goblet density in in aspirin group compared to control, T2 and T3 groups, while in contrast all these histomorphological parameters significantly($P<0.05$) increased in T3 group in compared to other groups.

Results of histomorphological measurements of intestinal mucosa clearly represent that aspirin cause shortening of villi high, losing villus apical structure, crypt

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