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Evaluation of the analgesic activity of new derivatives of aryl propionic acid on gastric male mice

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Available from: <http://dx.doi.org/10.21931/RB/CSS/2023.08.01.17>

ABSTRACT

This study focused on the recent synthesis of new compounds from aryl propionic acid derivatives compared to naproxen. The present study aimed to investigate the safety and efficiency of the new derivatives in improving analgesic effects and reducing adverse effects via modifying its chemical structure by adding new functional groups. The new compounds were characterized, and evaluate their pharmacodynamic effects. The analysis and characterization of new compounds were by ¹HMR and FT-IR spectrum. The investigation of the adverse effect after 5 days of remedy with 20 mg/kg daily administered with naproxen derivatives to the healthy male albino mice (25-30 g) for analgesic activity using the hot plate method. Mice were parted into 5 groups, consisting of the control group and 4 groups that administered naproxen or derivatives of aryl propionic acid (E, H, D1 and D2). The main tests are done by a hot plate, biochemical, macroscopic, and microscopic inspection. The results confirmed that the new drugs have potent analgesic activity. The results showed that mice administered with D1 expressed less ulcerative effect than parent naproxen, H, E and ethanol. Moreover, the number of lesions was significantly less in the D2 group, while D1-treated mice recorded no evidence of ulcers or hemorrhage in their stomachs after being examined under a dissecting microscope. The study concluded that the new D1 derivative is a compound worthy of research and future clinical applications due to its relatively high efficacy and low adverse effects compared to other derivatives prepared and tested in this study.

Keywords: Analgesic, Aryl propionic acid, Naproxen, Acidity

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines commonly used as analgesic and anti-inflammatory for humans and animals to relieve pain and

reduce inflammation and fever. They are ineffective in removing pain in the visceral organs; these effects are due to the strong inhibitory prostaglandins responsible for the sensation of pain and inflammation and the regulation of body temperature. A high dose of naproxen or prolonged use for a long period gives a chance of developing ulceration and bleeding in the stomach and gastro-duodenal injury 1. The clinical treatment used for preventing NSAID- injury on gastro-duodenal damage by traditional drugs such as proton pump inhibitors such as omeprazole effectively reduces gastro-duodenal damage². Ibuprofen 2-(4-isobutylphenyl) propionic acid is known as an NSAIDS. These derivatives have broad biological efficacy, including anticancer, analgesic, antibacterial, anticonvulsant, and anti-inflammatory activity 3-5. It was confirmed that gastrointestinal ulcer occurs in healthy volunteers taking NSAIDs in combination with proton pump inhibitors, and one study showed an increased elevation of the inflammatory bowel marker in patients taking proton pump inhibitors. New drugs should also be evaluated with parental naproxen for analgesia that exacerbates gastrointestinal damage caused by learning more about the potential gastrointestinal safety of drugs for treating inflammatory conditions. Naproxen is a phenyl propionic acid derivative with analgesic, anti-inflammatory, and antipyretic effects. This effect is believed to be mediated by inhibition of the prostaglandin synthetase complex with a subsequent decrease in the synthesis of prostaglandins from arachidonic acid 6. Naproxen has mild side effects compared to aspirin and indomethacin. The mechanisms by which (NSAIDs) cause gastrointestinal ulcers and bleeding are by destroying the surface barrier of tissues towards stomach acid and having a cytotoxic effect on the cell; on the other hand, NSAIDs reduce the defense mechanism such as mucus and bicarbonate layer blood flow. Cell renewal, prostaglandins, phospholipids, free radical scavengers 7. The mucous gel layer of the stomach and other parts of the gastrointestinal tract possesses non-wetting properties of the water table due to the synthesis and secretion of surfactant-like phospholipids. In addition, some studies reported that adding functional group phosphatidylcholine to naproxen showed significantly lower GI injury and bleeding in two systems of rodent models while improving anti-inflammatory and COX inhibitory activity 8, 9. The present study aimed to improve naproxen by increasing its analgesic effect and reducing its side effects by modifying the parent naproxen by adding a new functional group that generates new compounds with pharmaceutical activity rather than the parent compound.

MATERIAL AND METHOD

Animal study

Thirty healthy male albino mice weighing 25-30 g were obtained from the animal house of the pharmacology department of Veterinary Medicine College University of Baghdad, Iraq and distributed into six groups; each group included five mice placed in polypropylene cages. Animals were maintained at room temperature 25 °C and under environmental conditions for approximately 8–12 hours in the light-dark cycle). All animals were acclimatized for 10 days to animal house conditions before starting the experimental protocol, pellets and water ad libitum. After seven days of adaptation, mice were randomly divided into six groups, including group 1, A negative representation of the control group; this group was given only distilled water, while in group 2, naproxen was administered after an overnight fast, a single dose of the drug, mice received 20 mg/kg for analgesic effect. Group 3: After an overnight fast, mice received 20 mg/kg of H for analgesic effect. Group 4: After fasting, Animals (20mg/kg) received E for analgesic effect. Group 5: After an overnight fast, animals (20

mg/kg) received D2 for analgesic effect. Group 6: After an overnight fast, animals received 20 mg/kg D1 for analgesic effect. Mice were fasted from food but not water for 24 hours before the experiment. After the analgesic study ended, treatment persisted for six days. After 1 hour of treatment on the last day, these mice were anesthetized with a ketamine-xylazine cocktail (40 -10) mg/kg IP respectively 10.

Analgesic activity

The feet of mice are sensitive to heat from the hot plate at temperatures from 55°C to 60°C according to methods prescribed by 11.

Identification of macroscopic lesions

Mice were sacrificed using ether overdose, and the abdominal wall was incised longitudinally. The stomachs of mice were isolated and separated from the other surrounding viscera by two incisions: the first was made close to the cardiac sphincter, and the second was made away from the pyloric sphincter of the stomach. Then, the stomach was isolated and slightly distended by injecting formalin through the esophageal opening. The distended stomach was then immersed in neutral 10% formalin for 10-15 minutes to stabilize the inner and outer layers of the stomach wall. The stomach was opened along the greater curvature and rinsed briefly under continuous tap water. Then the mucosa was examined to determine ulcer parameters by dissecting a microscope (Zeiss AG in Jena, Germany).

Determination of gastric juice acidity

The acidity of gastric juice was estimated after the collection of all juice by using a pH meter apparatus.

Determination of gastric juice volume

Gastric juices were centrifuged by (Bioswisstec, Germany) at 500 rpm for 10-12 minutes and then separated and measured volume using an insulin syringe 12.

Histopathological examination

The stomachs of scratched mice were taken, washed with normal saline, and then immersed in 10% formalin solution. The fixed samples were trimmed, washed, and dried in ascending degrees of ethanol. Samples were then flushed in xylol, embedded in paraffin, cut 4–6 µm thick and stained with hematoxylin and eosin stain for gastrulation as described by 13.

Statistical analysis

All data of the experimental design were presented as mean± SEM. To compare between groups, we used the T-test for two group comparisons; multiple comparisons were performed using one-way ANOVA followed by the least significant difference (LSD) as a post hoc test. The 0.0001 level of probability was regarded as the criterion for significance. All statistical analyses were performed with the help of a statistical package for social sciences (SPSS) for Windows version 25 14.

RESULTS

Characterization of 2-(6-methoxy-2-naphthyl)-propionic acid.

The present study aimed to evaluate the efficacy of a new synthetic chemical agent derived from naproxen by adding a chemical group to standard naproxen to generate new drugs that have properties more preferable to standard naproxen through the ability to prolong sedation and good anti-inflammatory with minimum side effects than pure drug. Synthesis of New compound from Aryl propionic acid Interaction figure 1.

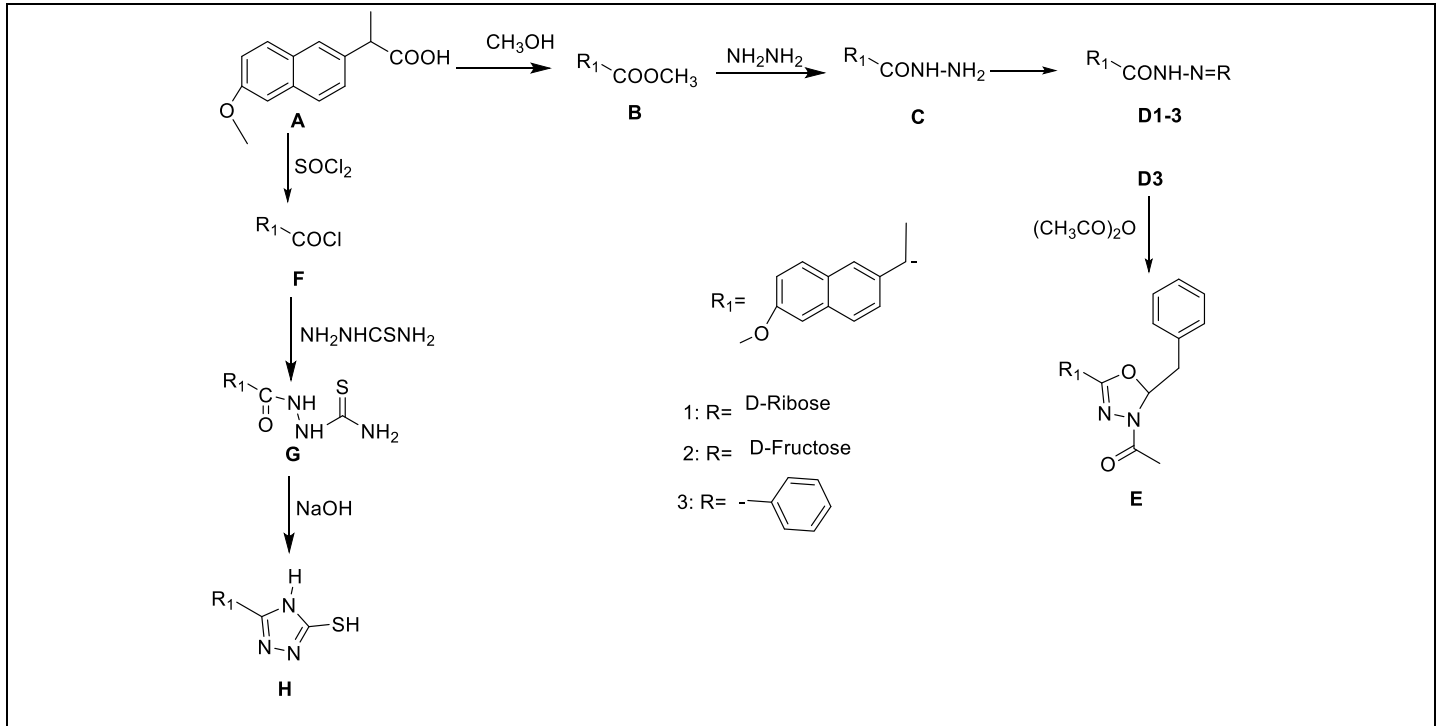


Figure 1: The new compounds are created from 2-(6-methoxy-2-naphthyl)-propionic acid (A).

Analgesic activity and quality of gastric contents

The pH values of Gastric juice in the treated mice with standard naproxen and different agents of modified naproxen were scheduled in Table 1. The results of the control group showed that the normal range at the level 6.16 ± 0.30 while the groups given a different oral agent of modified naproxen had a significant decrease at $p < 0.0001$ in the pH value of gastric juice in the H group (4.33 ± 0.21). The E groups that reached very low (2.83 ± 0.30) and D2 also decreased the PH value to (3.54 ± 0.34). On the other hand, the D1 group shows a value (6.16 ± 0.40) close to the control, and there is no significant compared to the control at $p < 0.0001$, and there is a significant difference between D1 and the other groups. Gastric juice volume in rats with standard naproxen and a different agent than adjusted naproxen is shown in Table 1 and Figure (2 and 3).

The results showed that gastric juice volume (cm³) as mean \pm SE for the orally given group (control group) was not significantly reduced (1.00 ± 0.04) at $p < 0.0001$ compared to the other naproxen group H, E and D2, respectively (0.65 ± 0.09 , 0.60 ± 0.08 , 0.37 ± 0.03 and 0.40 ± 0.03). Mice given oral D1 showed a significant increase in gastric juice volume to a level (0.98 ± 0.05) compared to mice given another chemical agent at the same dose; on the other hand, the D1 score showed very close to the control result and no significant differences between D1 and control. Naproxen at 20mg/kg dose significantly reduced the paw licking and paw jumping response (25.83 ± 0.65) compared to the control (6.66 ± 0.88). Other groups of compounds at $p < 0.0001$ also reveal the degree of inhibition of pain for H, E and D2. Respectively, D1 treated showed significant differences from standard naproxen, and the analgesia degree reached 43 ± 4.62 .

Groups	Rate pain reflex before analgesia in the second	Pain reflex after analgesia in second	Gastric juice volume in ml	pH of stomach
Control	6.00 ± 0.51 A	6.66 ± 0.88 D	1.00±0.04 A	6.16 ± 0.30 A
Naproxen	6.33±0.71 A	25.83± 0.65 B	0.65±0.09 B	3.50 ± 0.34 CB
H	6.00 ± 0.51 A	22.83±1.13 CB	0.60 ± 0.08 B	4.33 ± 0.21 B
D1	6.00 ± 0.57A	43±4.62 A	0.98±0.05 A	6.16 ± 0.40 A
E	6.00 ± 0.57A	26.00±1.39 B	0.37± 0.03 C	2.83± 0.30 C
D2	6.66 ± 0.56 A	17.66±0.71C	0.40 ± 0.03 C	3.54 ± 0.34 CB

Table 1. Evaluation of the analgesic effect by the hot plate method in male rats given orally standard-naproxen, another chemical-modifying agent of naproxen. Different superscript letters in the same column indicate the presence of highly significant differences below the level of probability 0.0001. Tested Compounds H, D1, E and D2 compared with naproxen.

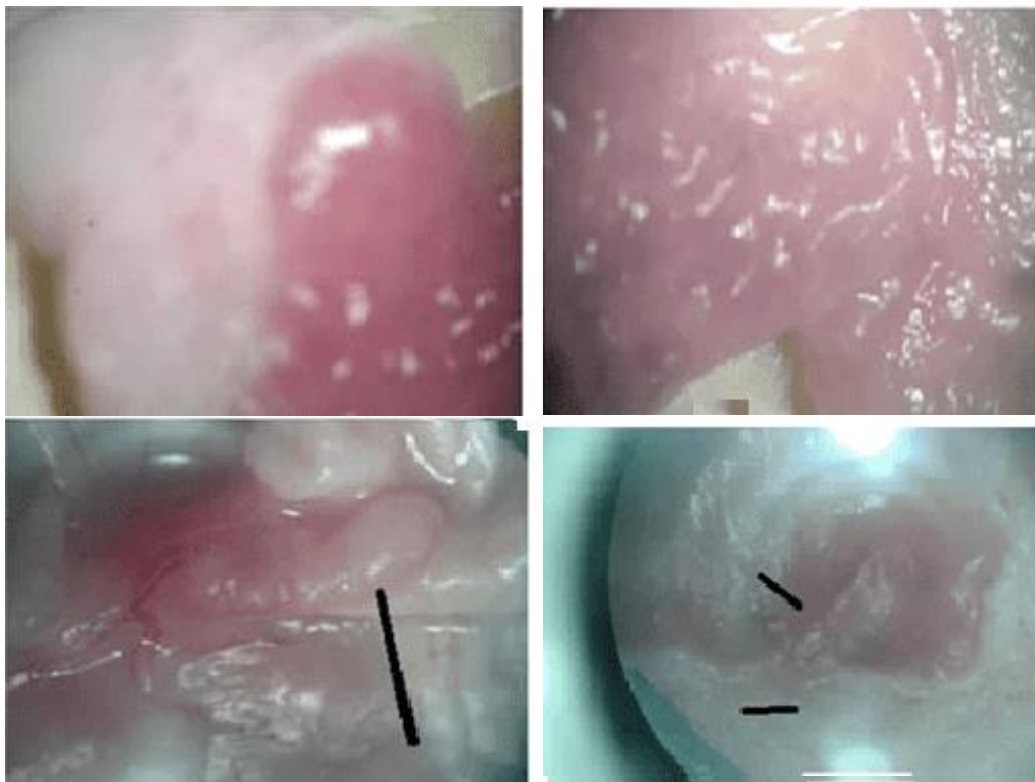


Figure 2. The effect of propionic acid derivatives on the gastric mucosa of mice.

Histopathological study

Histopathological section 6 refers to the control group of mice's small intestines showing normal histological stricture. (H&E 400X). On the other hand, figure 4 (A, B and C) refer to the stomachs of mice treated orally with 250 mg /kg of H for 5 days for the glandular region, showing inflammatory cell infiltration in the submucosal region (H&E 400X).

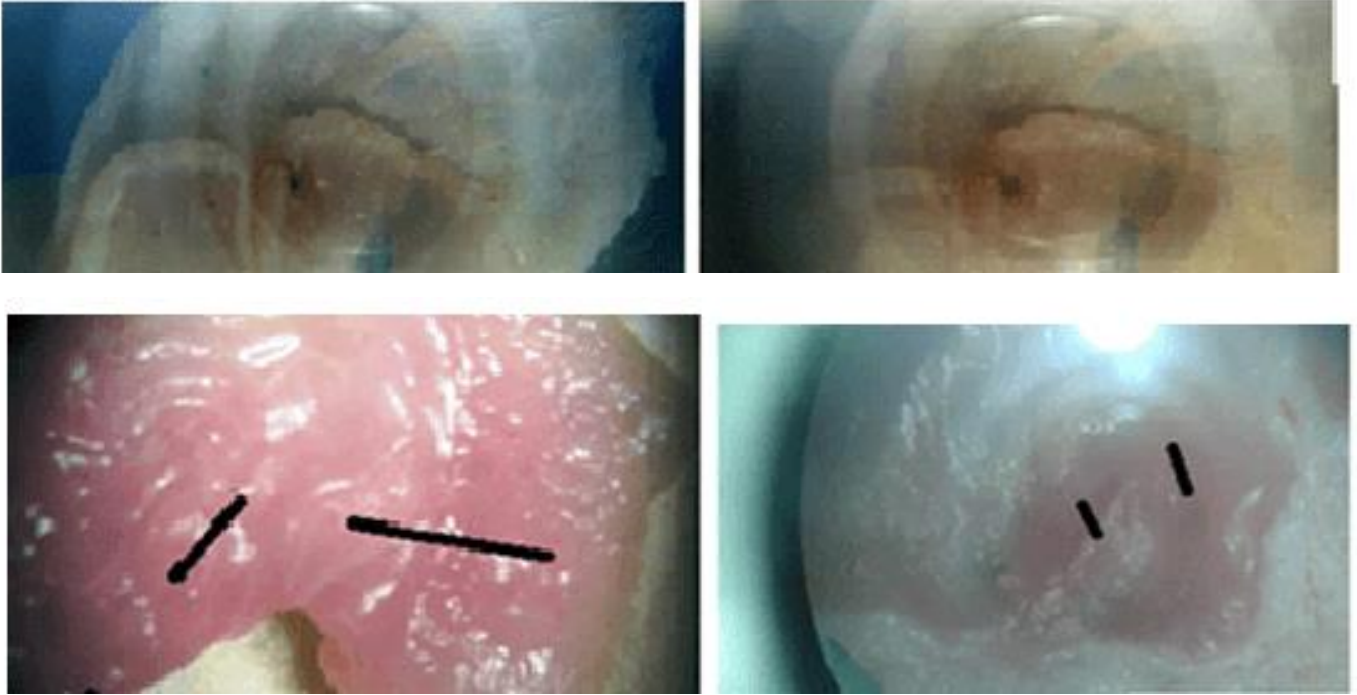


Figure 3. The effect of propionic acid derivatives on the gastric mucosa of mice.

The histopathological section in Figure 4 (D) shows severe ulceration and necrosis of the intestinal mucosa stomach of mice treated orally with naproxen for 5 days, showing acute gastric ulcer with hemorrhage and tissue debris in the lumen (H&E 100X). The effect was reduced in mice treated with new derivative H in Figure 4 (E and F) to appear congestion of blood vessels with inflammatory cell infiltration in the mucosa and submucosal layer, a non-glandular region showing hyperplasia and hyperkeratosis (H&E 100X).

The results in Table 1 demonstrated that there are no significant differences between all animal groups before analgesia; the present result shows all formulations have analgesic activity similar to or better than naproxen, while **the D1** group reveals a high significance with better analgesic activity than naproxen. These results showed a sharp change in gastric mucus permeability by a large volume of gastric juices (cm^3) in another group of naproxen **H**, **E** and **D2**, respectively. At the same time, the mice were given oral **D1**, a significant increase in the volume of gastric juice to the level as compared to mice that were given another chemical agent the same dose.

The advantages of the compound 6-methoxynaphthalene 2-yl (2,3,4,5-tetrahydroxyptilidine)-propane hydrazide have a good analgesic effect and uninduced ulcers at high doses may be due to inhibition of gastric acid secretion or showing 'cell-protective' activity by promoting local cell regeneration to maintain Mucous blood mucus flow and increased local production of mucus.

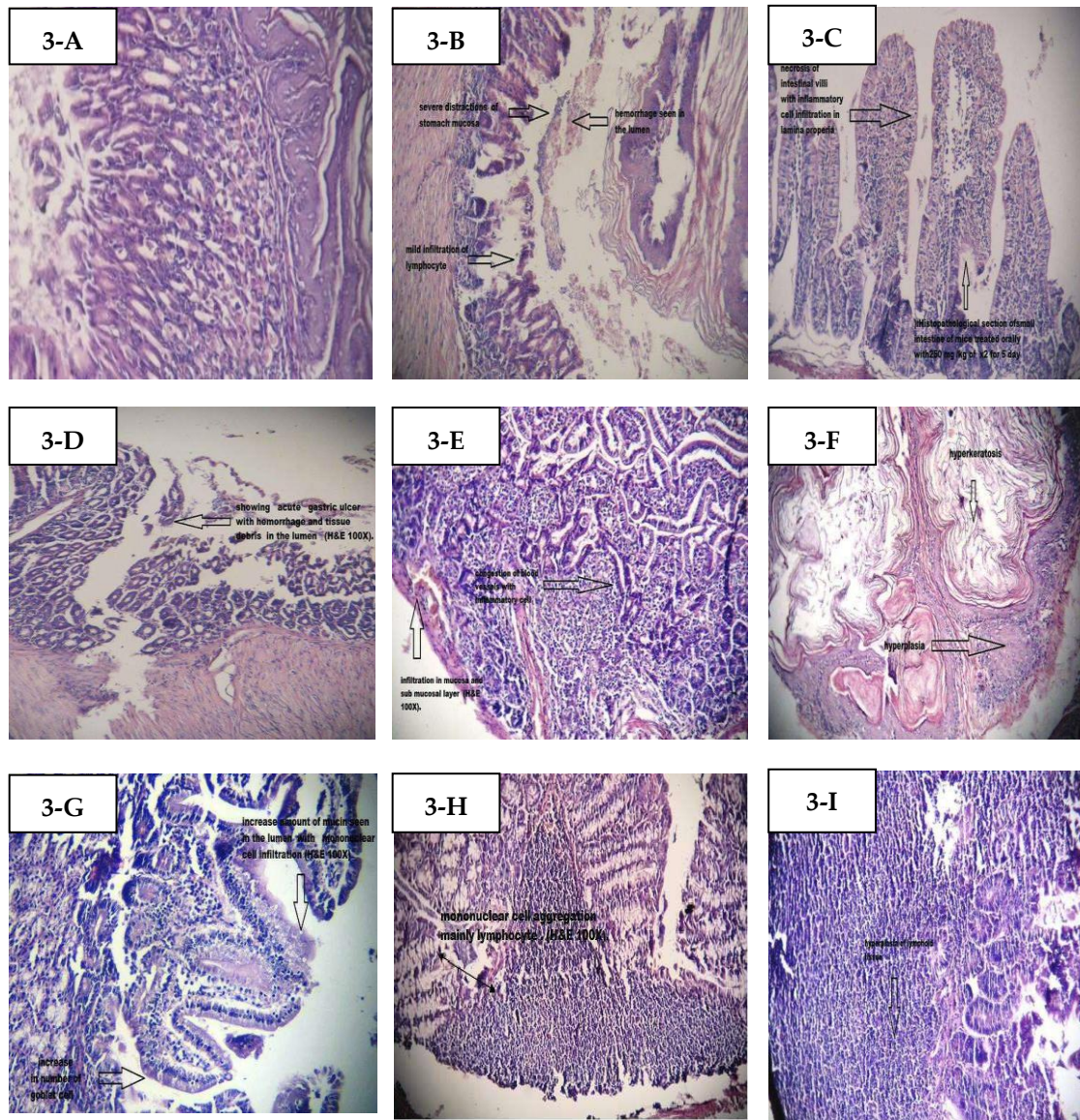


Figure 4(A, B, C, D, E, F, G, H, I): Histopathological section of small intestine of mice treated.

There is a significant difference between **D1** and the other groups, as the histopathological observations in this study showed no pathological changes in the stomach in the negative control groups in contrast to the stomach of the group caused by ulcers which shows severe changes ulceration and bleeding. Gastric hyperacidity and ulceration of the gastric mucosa occur mostly due to the medication by certain drugs and eating spicy foods for a long time. Moreover, the D-ribose to produce 6methoxynaphthalen-2yl)-N-(2,3,4,5-tetrahydroxypentylidene)propanehydrazide that pharmaceutical technology to agent give potent analgesic, with disappear ulcerogenic effect. Some studies showed that the formulation of naproxen with PC in an oil-based soy lecithin formulation has a degree of protection with an ulcerogenic effect rather than naproxen alone while possessing an analgesic effect and anti-inflammatory due to its intense COX inhibitory activity. Histopathological section of the small intestine of mice treated orally with 20 mg /kg of **D1** shows proliferation of epithelial cells and hyperplasia of gut association lymphoid tissue, indicating a complete healing process. The present study indicated that adding some material to naproxen increases the potency and efficacy in most chemical alterations.

However, **D1** is considered the best group in the potency of analgesic without gastrointestinal damage. Therefore, the study needed to increase research and clinical use on human patients.

DISCUSSION

The data indicate that the formulation agent increasing analgesic activity was in agreement with Lichtenberger, Barron¹⁵ indicated that Naproxen–Phosphatidylcholine (Naproxen-PC) revealed significant anti-inflammatory and COX-inhibitory activity and less GI injury and bleeding in two rodent model systems. Present results discussed above suggest that the COX inhibitory activity may be greater for modified naproxen than parent naproxen; it may have been highly effective in reducing pain sensation through potent inhibition of arachidonate cyclooxygenase and thus inhibition of the production of prostaglandins^{6, 16}. **D1** group, which is chemical name 6-methoxynaphthalen-2yl)-N-(2,3,4,5-tetrahydroxypentylidene)-propane hydrazide, is produced by the conversion of naproxen to phenyl hydrazine then addition D-ribose, that conversion may increase the potency of chemical compound leading to increase its activity¹⁷. indicate that a combination of 5-lipoxygenase inhibitors with naproxen potentiates the antinociceptive effect of naproxen, reducing the therapeutic dose and reducing side effects on GIT, Heart and renal that are popularly associated with NSAIDs. The new formulation of naproxen, especially **D1**, maybe an addition to the inhibitor effect on COX and may inhibit 5-lipoxygenase¹⁸. However, drug stimulation of peptic ulcers induces aggressive agents such as acid, pepsin, active oxidative stress, platelet exacerbating factor, leukotrienes, endothelium, and overproduction of hydrochloric acid and/or a decrease in gastric juice which has protective mechanisms¹⁹. Moreover, the harmful effect of prolonged use of drugs in chronic diseases leads to the formation of free radicals such as OH•, O2•-, RO•, and ROO, which play a role in causing stomach ulcers²⁰. The result showed congestion of blood vessels with hemorrhage and inflammatory cell infiltration in the mucosa and submucosal layer; the result was in concord with²¹, which is that indicates when the safety of the GI barrier is disturbed, the rate of back-distribution of gastric acid and pepsin increases, leading to irritation, ulceration, inflammation and hemorrhage²². This result was in agreement with²³, which indicates the addition of polyethylene glycol and polyvinyl pyrrolidone to meloxicam showed a significant increase in anti-inflammatory effect in rodents paw edema induced by carrageenan compared to meloxicam alone. Physical mixture and solid dispersion of some drugs possess the best analgesic and anti-inflammatory properties with minimum ulcerogenic potential as compared to parent drugs^{8, 24}, was indicated that the therapeutic potency and efficacy of Ibuprofen-phosphatidylcholine (PC)-used for inhibiting pain/inflammation in patients with osteoarthritis and compared to that parent ibuprofen, for 6-week in patients with osteoarthritis result profit there is mild side effect on GIT in a patient treated with PC than parent ibuprofen. Likewise, in case of ulceration, initiation of progenitor cell proliferation is accomplished by two actor growth factor alpha (TGFα) and insulin-like growth factor 1 (IGF-1); in case of gastric ulcers, IGF-1 activates polymerization, cell proliferation, re-epithelialization, and induced COX-2 in a phosphatidylinositol 3-kinase-dependent manner²⁵. Growth factors and nitric oxide (NO) affect GI epithelium proliferation. It is a very important healing process, and there is limited activity after treatment with NSAIDs²⁶.

CONCLUSION

This study reveals that pharmacological tests performed in the present research suggest that all new drugs possess potent analgesic activity but vary from one compound to another and demonstrate **that the D1** naproxen derivative is more potent and a worthy focus for future research and possible clinical implementation due to its comparatively high efficacy and low side effects in comparison to other drugs tested in this study

Funding: self-funding

Competing interests

The authors have not declared any conflict of interest.

Ethical consideration

Ethical issues (including plagiarism, consent to publication, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) were verified by all authors.

Authors contribution

Conceptualization, SA and SJH; methodology, SA and MEA.; software, SA; validation, AMM, HKK and NHC.; formal analysis, HHK; investigation, MJJ; resources, HAJ; data curation, AMJ; writing—original draft preparation, HHK; writing—review and editing, HHK; visualization, MEA; supervision, AMJ; project administration, RH; funding acquisition, HTA. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

We thank the Department of Pharmacology and Biochemistry in Veterinary Medicine, Al-Qasim Green University, Babylon, Iraq, for cooperation in preparing this study for publication.

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Received: 26 September 2022 / Accepted: 15 October 2022 / Published:15 February 2023

Citation: Sadiq Al-Mansury , Mohammed R. Obaid , Saadeya A. Al-Gnami , Mohammed J. Jawad , Hussein A. Ghanimi ,Adnan M. Jassim , Hawraa T. Abass, Rusul Heider , Hamzah H. Kzar , Moaed E. Al-Gazally. Evaluation the analgesic activity of new derivatives of aryl propionic acid on gastric male mice. *Revis Bionatura* 2023;8 (1) 17. <http://dx.doi.org/10.21931/RB/CSS/2023.08.01.17>