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Science Journal of University of Zakho

Vol. 5, No. 1, pp. 48 –52, March-2017

p-ISSN: 2410-7549
e-ISSN: 2414-6943

CURATIVE EFFECTS OF POMEGRANATE AND GINGER ON HEPATIC AND RENAL FUNCTIONS OF INDOMETHACIN-INDUCED PEPTIC ULCERS IN ALBINO RATS

Mudhir S. Shekha [a, b,*] Muhsin J. Abulwahid [b]. Peshraw S.Hamadamin [a], Trifa F. Ismail [c], Saman R. Hamad bakir [d]. Laween M. Ibrahim [e], Lana M. Ahmed [a]

[a] Dept. of Biology, College of Science, University of Salahaddin, Kurdistan Region - Iraq.
[b] Research Center, University of Salahaddin, Erbil, Kurdistan Region - Iraq.
[c] Dept. of Biology, College of Education, Salahaddin University, Kurdistan Region - Iraq
[d] Hareer Hospital, Erbil Directorate General of Health, Ministry of Health, Kurdistan Region - Iraq.
[e] Rapareen Children Hospital, Erbil Directorate General of Health, Ministry of Health, Kurdistan Region - Iraq.

Received: Nov. 2016 / Accepted: Feb. 2016 / Published: Mar. 2017 ***https://doi.org/10.25271/2017.5.1.300***

ABSTRACT:
A peptic ulcer is one of the more severe diseases and most classic treatment protocol produce adverse drug reactions. Therefore, this study aimed to examine the therapeutic effects of two natural extracts, namely Pomegranate and Ginger, on indomethacin-induced gastric ulcer in rats. Animals were divided into five groups; 1. Normal control group, 2. An ulcer control group Indomethacin (0.3 mg /rats), 3. Omeprazole (3 mg /rats), a4. Pomegranate (40 mg /rats), 5. Ginger (20 mg /rats). The ulcers were induced made from groups 2 - 5 by oral administration of Indomethacin. Rats subjected to indomethacin administration showed significant ulceration in the glandular area of their stomachs compared to normal control rats. In addition, significant elevations S.GPT, S.GOT, S. creatinine and S. Urea ($P< 0.05$) were observed. Alternatively, pretreatment with pomegranate and ginger significantly corrected macroscopic and biochemical parameters. These results demonstrate that administration of either pomegranate and ginger supplementation have an essential role in the prevention of ulceration induced by NSAIDs. Furthermore improved liver and kidney functions and reduced hepatoto and nephrotoxicities.

KEYWORDS: Peptic ulcer, Ginger, indomethacin, hepatic and renal functions, rats.

1. INTRODUCTION

Peptic ulcer diseases comprising gastric and duodenal ulcers which are the most prevalent gastrointestinal disorder. The pathophysiology of ulcer involves an imbalance between offensive (acid, pepsin, H. Pylori and non-steroidal anti-inflammatory agents) and defensive factors (mucin, prostaglandin, bicarbonate, nitric oxide and growth factors) (El-Metwally, 2014). A peptic ulcer occurs in that part of the gastrointestinal tract which is exposed to gastric acid and pepsin, i.e., the stomach and duodenum. It may be resulted from an imbalance between the aggressive and the defensive factors (S Bhattacharya et al., 2007 July 21).

Indomethacin is a non-steroidal anti- inflammatory drug (NSAID) with anti-inflammatory, antipyretic, and pain-relieving properties, which is known to produce erosions, ulcerative harm, and petechial bleeding in the mucosa of the stomach as a severe side effect. The oral administration of Indomethacin in rats cause ulcerative lesions in the gastric mucosa, which is mainly mediated through generation of oxygen free radicals and lipid peroxidation (Srinivas, 2011)
Concern about the effects of various foods on human health has risen significantly in recent years. And that plant-based foods, including fruit and vegetables, are regarded as essential for human health (Hamauzu, 2011). Pomegranate is used in the folk medicine in different Asian societies for the treatment of a type of infirmities. In India, Tunisia, and Guatemala, dried Pomegranate peels are decocted and manipulated both internally and externally as astringents and antiseptics and used for treating apathies and diarrhea (Elisa Colombo, 2013)
Therefore the intention of the current study is to examine whether pomegranate peel extract consumption has curative effect toward gastric ulcers and may be helpful in the prevention of Indomethacin-induced ulcer genesis.

2. MATERIALS AND METHODS

2.1 Materials (Chemicals and Tested Compounds)

Indomethacin (50 mg ampoules) were obtained from local pharmacy, the peel, rind of the P. granatum Linn. (Variety arak) was procured from the local market of Erbil. The dose for rat was 0.33 mg/kg bow orally given once after 24 hour of fasting. Omeprazole as chemical treatment for stomach they were obtained from local pharmacy and mixed with distilled water, omeprazole and Indomethacin doses 3mg /kg D.W and 0.33mg/kg D.W respectively.

2.2 Methods

2.2.1 Experimental animal: The present study was carried on (25) adult albino male rats procured from Department of Biology Animal House, weighing (150-200 g). Animals were housed in environmentally established conditions (temperature of 22 ± 2∘C) with a 24 hour.
2.2.2 Experimental design: Twenty five male albino rats were classified into five groups (5 rats in each group) as follow:
Group I: Served as a control and were supplied with normal feed and water.
Group II: Received 0.3 mg/ rats of Indomethacin.
Group III: Received 3 mg/ rats of omeprazole.
Group IV: Received 40 mg/ rats of pomegranate.
Group V: Received 20 mg/rats of ginger
The ulcers were induced in groups 2 to 5 by oral administration of Indomethacin .The Rats were fasted for 8 hours prior to the experiment. All the drug solutions were given 8 hour after Indomethacin administration and the tested plants were given

with food and lasted for a period of 5 days. At the end of experimental period, animals were kept fasting for 24 hours before blood sampling, blood was withdrawn from Heart by using capillary tubes and collected in clean tubes.

2.3 Determination of biochemical parameters

After anesthesia of the rats by ketamine and xylazine (40 mg/kg and 10 mg/ kg), blood samples were collected from heart, centrifuged at the rate of 3000 rpm for 20 min. The isolated sera were transferred to the laboratory for measurement of liver function Test (glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT)) and Kidney Function test (Creatinine, Urea, Uric Acid). To measure liver enzymes and Kidney function tests, were analyzed calorimetrically according to Richmond method.

2.4 Statistical analysis

The results were presented as means ± S.E.M and comparison between the experimental groups were made using Dunnet test and ANOVA. (*: P<0.05, **: P<0.01, ***: P<0.001) were considered as indicative of significance by using GrphaPad prism 7.1

3. RESULTS

Rats subjected to indomethacin administration showed significant ulceration in the glandular area of their stomachs compared to normal control rats. Pretreatment with pomegranate, ginger and Omeprazole significantly reduced ulceration and significantly prevented the incidence of ulceration as compared to ulcer control group as shown in figure 1. Rats subjected to indomethacin administration (ulcer control rats) showed significant increase in S.GPT and S.GOT (P< 0.05) whereas pomegranate, ginger and Omeprazole significantly decreased in S.GPT and S.GOT when comparing with indomethacin group (P<0.05-0.01) as shown in figures 2 and 3.

Indomethacin administration produced significant increases in serum creatinine (P<0.05) in Rats of indomethacin Gastric Ulcer Model. On the other hand pomegranate and ginger significantly decreased in S. creatinine when comparing with Indomethacin group (P<0.001) as shown in figure 4. Indomethacin induced gastric ulcer significantly increased S. Urea (p<0.05) while pomegranate and ginger significantly decreased in S. Urea when comparing with Indomethacin group (P<0.05) Figure 5.

Results showed that indomethacin induced rat, no significant (P<0.05) differences was observed in Uric acid level between ulcer and other four groups (Figure 6)

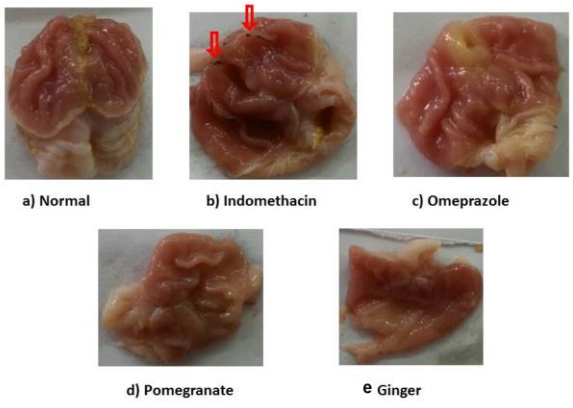

Figure.1. Macroscopic appearance of gastric mucosa in the (a) Control group, (b) Indomethacin treated group (IND), (c) Omeprazole group, (d) Pomegranate, and (e) Ginger group.

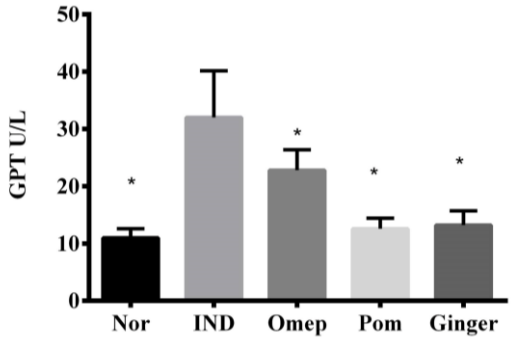

Figure 2. The activity of (GPT) value for the effect of the treatment in rats with Indomethacin –induced gastric ulcer. The activity of GPT in control, indomethacin induced ulcer and other groups. Results are presented as Means ± SEM.

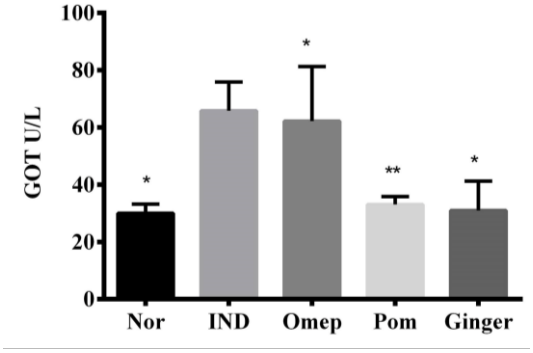

Figure 3. The activity of (GOT) value for the effect of the treatment in rats with Indomethacin –induced gastric ulcer. The activity of GOT in control, indomethacin induced ulcer and other groups. Results are presented as Means ± SEM.

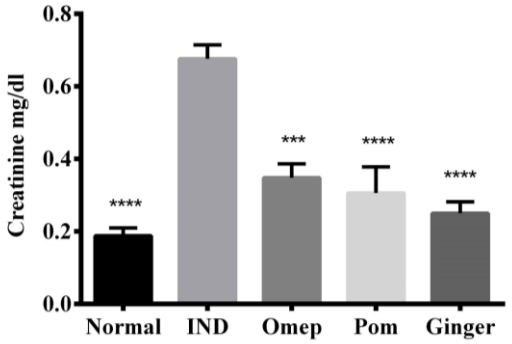

Figure 4. The activity of (Creatinine) value for the effect of the treatment in rats with Indomethacin –induced gastric ulcer. The activity of Creatinine in control, indomethacin induced ulcer and other groups. Results are presented as Means ± SEM.

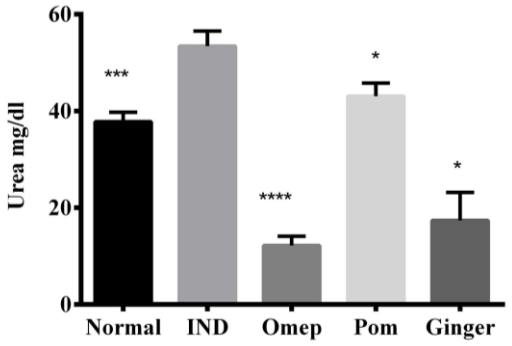

Figure 5. The activity of (Urea) value for the effect of the treatment in rats with Indomethacin –induced gastric ulcer. The activity of Urea in control, indomethacin induced ulcer and other groups. Results are presented as Means ± SEM.

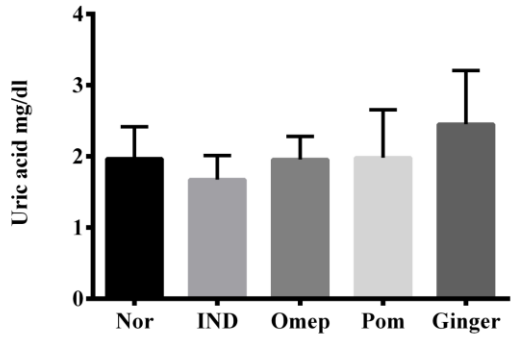

Figure 6. The activity of (Uric acid) value for the effect of the treatment in rats with Indomethacin –induced gastric ulcer. The activity of Uric acid in control, indomethacin induced ulcer and other groups. Results are presented as Means ± SEM.

4. DISCUSSIONS

The present investigation aims to evaluate the possible Curative effects of pomegranate and ginger on indomethacin-induced gastric ulcer in rats. Results of the current study revealed that indomethacin administration caused significant ulceration in the glandular area of the rat stomach as seen during macroscopic examination. These results are in compatible with previous examinations demonstrating that anti-inflammatory drug like indomethacin can produce visible gastric ulcers in experimental animals (Heeba et al., 2009, Zaghlool et al., 2015). On the other hand, mechanisms for such actions of NSAIDs seem to be complex and multifactorial, including the inhibition of prostaglandin synthesis, induction of apoptosis and necrosis of gastric mucosal cells (Hoshino et al., 2003, Redlak et al., 2005).

Results of the current study showed that pomegranate treated animals from indomethacin-induced gastric ulceration as manifested by significantly reduced ulceration area. Similar results that were achieved by previous authors (Hussein et al., 2014, Moghaddam et al., 2013) indicating a high antiulcer activity of pomegranate on indomethacin-induced ulcers. Pomegranate induced an increase in mucus production which was most demonstrative in indomethacin treated rats. Mucus serves as the first line of the defense against ulcerogenic (Hussein et al., 2014).

According to present study, ginger significantly reduced the ulceration after indomethacin administration. Earlier, ethanolic extract of ginger produced a significant decrease in the intensity of ulceration induced by indomethacin and aspirin (al-Yahya et al., 1989). The ethanol extract of ginger showed a high anti-inflammatory activity against acute inflammation, suppressing the rat paw edema both at the early and later phases, though not dose-dependently (Anosike et al., 2009). Previous reports by Agrawal et al. and Mohsen et al. (Agrawal et al., 2000, Mohsen Minaiyan et al., 2006) on the anti-ulcerative activities of ginger suggest that ginger extract possesses its anti-ulcerative properties through a mechanism related to acid and pepsin secretory inhibition.

In the present investigation, indomethacin administration significantly increased liver enzymes compared to normal rats and omeprazole group, again in harmony with previous studies demonstrating that indomethacin administration produced a significant increment in S.GOT and S.GPT (Falzon et al., 1985, Sanchez-Ramirez et al., 2001) . High doses of indomethacin in rats cause a substantial decrease in the hepatic microsomal cytochrome P-450 -dependent monooxygenase enzyme system, which has the responsibility of metabolizing drugs and many other chemicals (Falzon et al., 1985), and thus it is not amazing that increased serum levels of S.GOT, a marker of cellular damage, are observed.

Serum GOT was lower in all the groups treated with indomethacin plus omeprazole, pomegranate, and ginger. These results provided evidence that pomegranate and ginger are able to improve hepatic steatosis in rats without obvious hepatotoxicity. Additionally, this research revealed that Pomegranate modified the protecting influence of antioxidant status and liver damage. These results are apparently related to its phenolic compounds and linolenic acid contained in this fruit (Sadeghipour and Eidi, 2014). The antioxidant activity of phenolics and linolenic acid are essentially due to their redox features, which allow them to act as reducing agents, hydrogen donors, singlet oxygen quenchers, and metal chelators (Rice-Evans et al., 1995, Sadeghipour and Eidi, 2014). It had been reported that the bioactive component of ginger, namely gingerol and antioxidative effect by inhibiting peroxidation of phospholipids induced by xanthine oxidase activity also inhibit prostaglandins and leukotriene synthesis (Chang et al., 1994, Nurtjahja-Tjendraputra et al., 2003).

Nonsteroidal anti-inflammatory drugs are used widely in clinical medicine. In spite of their therapeutic utility, however, they are known to cause notable gastrointestinal and renal toxicities, circumstances that limit their use (Basivireddy et al., 2004). The renal effects of NSAIDs include electrolyte imbalance, acute renal failure, a nephrotic syndrome associated with interstitial nephropathy and papillary necrosis (Grom, 1986).

Creatinine is produced in the body from the breakdown of creatine phosphate in muscle and is ordinarily produced at a reasonably regular rate by the body depending on muscle mass (Zuo et al., 2008). Creatinine is a commonly used as an indicator for kidney function. Urea is a primary nitrogenous end product of protein and amino acid catabolism, produced by the liver and distributed throughout the intracellular and extracellular fluid (Corbett and Banks, 2013). In the present study, we found that damage to the kidney was characterized by higher serum creatinine level in indomethacin-treated rats compared to normal control rats, but treatment with pomegranate in indomethacin-treated rats significantly reduces the elevated serum creatinine level in a dose-dependent fashion. On the contrary, pomegranate supplementation decreased generation of free radicals or ROS, suppressed the renal MDA level and increased antioxidant enzyme activities (GSH, SOD) in renal tissue. These findings substantiate the antioxidant activity of pomegranate which established in other nephrotoxic models such as

gentamicin- induced nephrotoxicity (Cekmen et al., 2013, Sadeghi et al., 2015). Thus, it can be hypothesized that the protection afforded by pomegranate in this study could be attributed to its antioxidant effect and this finding is in harmony with the earlier reports in which it has been reported that supplementation with antioxidant and anti-inflammatory agents suppresses renal damage caused by cisplatin (Kilic et al., 2013, Ueki et al., 2013)

Indomethacin treated rats with ginger extracts recorded a significant decrease in serum urea and serum creatinine levels as compared to indomethacin group (Group 2); Which provide a further comfort to the role of the extracts in reducing byproducts and as antioxidant. These findings were in agreement with Mehrdad et al. (Mehrdad et al., 2007) who stated that ginger has a favorable effect on the removal of urea and creatinine from a plasma of normal mice treated with its alcoholic extract and considered as a healing herb to manage renal function.

5. CONCLUSION

In conclusion, the results of this research revealed that pomegranate and ginger supplementation have an essential role in the prevention of ulceration induced by NSAIDs also improving liver and kidney function and reducing hepatotoxicity and nephrotoxicity

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کورتیا لێکولینێ:

برینی گەدە یەکێکە لە نەخۆشیە سەختەکان. زۆربەی چارەسەر کلاسیکەکان کاردتنەوەی زیان بەخشی دەبێت. لەبەر ئەوە ئەو لێکۆلینەوەمان ئەنجام دا تا کاریگەری چارەسەری هەنار ە زەنجەفیل لەسەر برینی هاندراو بە ئیندۆمیساسین لە جورج. گیانەوەران دابەش کران بۆ پێنج گروپ: گروپی ئاسایی کۆنترۆل، گرۆپی لەسەر برینی هاندراو ئیندۆمیساسین (0.3 ملگم/ جورج)، ئمیپرازۆل (3 ملگم/ جورج)، هەنار (40 ملگم/ جورج) و زەنجەفیل (20 ملگم/ جورج). برینی گەدە هاندەدرێت بۆ گروپەکانی 2 تا 5 بە پێدانی ئیندۆمیساسین بە رێگای دەم. ئەو جورجانەی ئیندۆمیساسینیان پێدرا تووشی برین بوبون لە رووبەری رژینەکانی گەدەکاتێك بەراوردی دەکەین لەگەڵ کۆنترۆل. لەگەڵ ئەوەش بوە هۆی بەرزبوونەوەی رێژەی GPT و GOT و کریاتینین و یۆریای سیرەمی خوێن ($P< 0.05$). لەسەرێکی ترەوە پێدانی هەنارە زەنجەفیل لەگەڵ ئیندۆمیساسین بە تەواوی چارەی کردوە لە بواری ماکرۆسکۆپی و بایۆکیمیاوی. ئەنجامەکەمان وا نیشان دەدات کە پێدانی هەنارە زەنجەفیل رۆلێکی سەرەکی هەیە لە قەدەغەکردنی دروست بوونی برینی گەدە بە NSAIDs هەروەها جێترکردنی کرداری گورجیلك و جگەر و کەمکردنەوە ژەهراوی بوونی گورجیلك و جگەر.

خلاصة البحث:

قرحة المعدة هي أحد الامراض الحادة و معظم العلاجات الكلاسيكية تنتج أضرار جانبية. لذلك تهدف هذه الدراسة دراسة الآثار العلاجية لاثنين من مستخلصات طبيعية، وهي الرمان والزنجبي على قرحة المعدة التي يسببها الاندوميتاسين في الجرذان. . تم تقسيم الحيوانات إلى خمس مجموعات. 1. مجموعة كونترول طبيعية ، 2. مجموعة قرحة اندوميثاسين (0.3 ملغم / الجرذان)، 3. أوميبرازول (3 ملغ / الجرذان)، الرمان (40 ملغ / الجرذان)، 5. الزنجبيل (20 ملغ / الجرذان). وقد يتسبب في تقرحات مصنوعة من الجماعات 2-5 عن طريق الفم من الإندوميتاسين . وأظهرت الجرذان المعرضة اندوميثاسين تقرح كبير في منطقة غدي من امعائهم مقارنة بالمجموعة الكونترول. وبالإضافة إلى ذلك، لوحظت ارتفاعات كبيرة في سيرم GPT ، GOT، الكرياتينين واليوريا ($P <0.05$) . بدلا من ذلك، المعالجة مع الرمان والزنجبيل تصحيح كبير المعلمات العيانية والكيمياء الحيوية. هذه النتائج اثيتت أن الرمان و الزنجبيل لهما دورا أساسيا في الوقاية من تقرح الناجم عن مضادات الالتهاب غير الستيروئيدية. وعلاوة على ذلك تحسين وظائف الكبد والكلى و تقليل من تسمم الكلى و الكبد.