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The Gastroprotective Effects of Papaya Seed Crude Extract on Aspirin Induced Gastric Ulcer in Mice

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Abstract

The seeds of *carica papaya* fruit have been studied for its gastroprotective action on patients with gastric ulcer due to its rich phytochemical constituents that have strong antioxidants and anti-inflammatory activity. The seeds of the newly cultivated in Iraq *c.papaya* plant were collected and extracted via Soxhlet apparatus using 70% aqueous ethanol. The ethanolic extract was phytochemically investigated to show the presence of flavonoids, phenolic compounds, alkaloids and saponins. Our in-vitro study model of the gastro protective action of the seed extract used aspirin for the induction of oxidative stress mediated ulcerative lesions in gastric mucosa of mice. Ulceration index (%) and acid output, pH, and gastric volume, oxidative stress levels and Proinflammatory cytokines (TNF) are the biochemical parameters measured in our assay. It was found that *c.papaya* extract decreased the level of ulceration index (39.67%) as compared with aspirin (121.34%) and (28.12%) of famotidine treated mice. In addition, the *c.papaya* seed extract showed statistically significant decrease ($p < 0.05$) in acid output, pH, and gastric volume, oxidative stress levels (MDA and SOD) and Proinflammatory cytokines (TNF) as compared with Aspirin treated mice. Further isolation of *c.papaya* phytochemical constituents is promising to identify additional pharmacologic actions

Keywords: Gastroprotection, Papaya extract, aspirin, ulcer.

INTRODUCTION

In the last decade herbal and natural resources have been a rich source of research for new remedies and treatments. Herbal products have shown a huge leap globally as consumers favor them in disease prevention and they have been a popular choice for many when it comes to treating disease. Increase in global use and interest in herbal supplements and remedies thus research in this field is a nonstop pursuit to prove their effectiveness [1]. Gastrointestinal issues, particularly gastric ulcers, remain to be a major health concern for many, as the possible causes remain to be increasingly widespread among people [2]. Regardless of genetic origin, external predisposing factors remain a concern such as the increased use of non-selective non-steroidal anti-inflammatory medications and the use of aspirin prophylaxis in addition to helicobacter -pylori which requires a strict treatment regimen. [3,4] Studies reported the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on gastric mucosa leading to oxidative stress in multiple ways. NSAIDS are cox inhibitors thus causes reduction of gastric prostaglandin which will contribute to peptic ulcer pathogenic process since prostaglandin has a protective role on stomach wall. The latter role as well as the production of reactive oxygen species all contribute to the damage and cell death on gastric wall [5,6]. The seeds of *carica papaya* tropical fruit have been investigated for its antiacid and anti-pepsin activity finding its significance to help in treatment of gastric ulcers, in fact the gastroprotective effects of the seed extract have been proven by several invitro studies [7,8]. Nonetheless the anti-inflammatory and anti-microbial properties of the extract have shown synergistic benefits in gastric ulcer prevention and treatment [9,10]. Many chromatographic and antioxidant assays showed that seed extract is rich with polyphenolic compounds and flavonoids like quercetin and caffeic acid [11,12] and have been involved in the protective anti-ulcer activities [8,9,13], by aiding in soothing gastric mucosa and preventing oxidative damage that contributes in gastric ulcer [14]. Interestingly *carica papaya* has successfully been cultivated in Iraqi environment though it's known to be native to tropical areas.

Thus, this study aims to evaluate the gastro-protective actions of *carica papaya* seeds extract and

phytochemically investigate it to identify some of the active phytochemical classes.

MATERIALS AND METHODS

The seeds of *carica papaya* were collected, cleaned and air dried for seven days. Twenty grams of seeds were defatted using petroleum ether for 24 hours and then allowed air to be dried. The twenty grams of seeds were crushed and ready for extraction by 300 milliliters of 70% aqueous ethanol using Soxhlet apparatus for 6 hours. The crude alcoholic extract was concentrated under vacuum rotary evaporator [15-17].

Preliminary Phytochemical analysis

The chemical tests applied on the crude extract are Mayers test, sodium hydroxide, and ferric chloride foam test to detect the presence of alkaloids, flavonoids, phenolic compounds and saponins respectively [18,19].

Invitro anti-ulcer design

Forty male albino mice, with a weight ~25 g, supplied by the animal House of Faculty of Pharmacy, Al-Nahrain University (Baghdad. Iraq). The animals were put in appropriate crates and set to adapt to laboratory circumstances for one week prior to the experiments. Temperature of twenty five degrees (25 °C) and 12 hour light-dark cycle was conserved. Metabolic cages were prepared for mice having raised floors of wide mesh to prevent coprophagia, that can influence gastric ulcer induction. Food was not given to the animals for one day (24 hrs.) to evacuate the stomach from food and increase the level of gastric acid, this helps assist injury of gastric mucosa when aspirin is administered. Water was suspended one hour prior to the experiment. Injury in the gastric mucosa was induced by an oral dose of Aspirin (500 mg/kg body weight). The animals were randomly allocated to four groups (n = 10). Group 1 control group. Administered distilled water. Group 2 (ulcer induction group) received a single oral dose of aspirin 500 mg/kg both [20]. Group 3 and 4 was treating with famotidine 30 mg/Kg orally and the extract of at dose 600mg/kg orally for 10 days, respectively at day 10 both groups administrated with single oral dose of aspirin 500 mg/kg.

Sample collection

After the last dosing, the mice kept fasting overnight. Next day, the mice were anesthetized using diethyl ether and weighed. The stomachs were sliced open along the larger curvature, and the contents were collected in tubes for biochemical analysis, then these stomach contents were centrifuged for 5 minutes at 3000 rpm. After being separated, the supernatant's volume was expressed as ml/100 g of body weight. Then carefully rinsed the stomach in ice-cold (PBS; pH 7.2–7.4) to remove any blood clots or contents. Subsequently, the stomachs were positioned where the surface of mucosal layer is upright on a wax plate sealed by filter paper. Then photographs were taken digitally of the stomachs intended for macroscopical investigation.

Finally, all stomachs were fragmented into smaller pieces then on ice a homogenizer was use for homogenizing in a precise volume of PBS (about one gram of tissue to nine milliliters). Then, to further damage cell membranes, two freeze-thaw cycles were applied to the suspension [21] Subsequently, the homogenate was centrifugated at 5000 rpm for fifteen minutes to measure the indices of oxidative stress which are MDA and SOD1 levels as well as, the inflammatory cytokines Tumor necrosis factor TNF-α using enzyme-linked immunosorbent assay (ELISA; Elabscience).

The ulceration index (%) of Gastric mucosal ulcers were scored as follows: 0: normal colored stomach; 0.5: hyperemia; 1: spot ulcer; 1.5: hemorrhagic streak; 2: deep ulcers; 3: perforation. The ulcer score was then calculated as the mean of ulcers in each group, then the ulcer index (UI) was obtained by multiplying the ulcer score by 100. The prevention percentage was calculated as: [(UI control-UI test) /UI control] × 100. [22] Acid output, pH, and gastric volume, oxidative stress levels and Proinflammatory cytokines (TNF) level are the parameters assayed for experimental animals.

The statistical analysis

The records were conveyed as mean values plus standard error of means. The means of two groups were compared using unpaired t-test, and the means of three groups or more were compared by ANOVA (analysis of variance). Statistical Package for Social Sciences (SPSS; version 23) was employed in the analysis of the results. When a p-value is less than 0.05, this was considered significant.

RESULTS

The phytochemical analysis of the alcoholic seed extract produced the results shown in the table below, the test results show the presence of flavonoids, alkaloids, phenolic compounds and saponins accordingly. These results are in accordance with the active compounds in literature for *carica papaya* seed extract.

Table 1: preliminary phytochemical test results of *carica papaya* seed extract

Test	Result
Alkaloids (Mayer test)	+
Flavonoids (NaOH test)	+
Phenols (Ferric chloride)	+
Saponins (Foam test)	+

The gastroprotective effect was assayed and the biochemical parameters measured gave the following results.

Table 2: Ulceration index in the experiment groups

Group	Ulceration index %
Control	0
Aspirin	121.34
Famotidine + Aspirin	28.12
c.papaya Extract +Aspirin	39.67

The stomach wall was more fragile and thinner when compared to the wall in control group in mice on Aspirin. In the glandular area lesions with varying shapes from spot ulcers to hemorrhagic lacerations layered with blood clots (ulcer index: 121.34). The stomachs of mice were grossly examined, and the glandular area was shown to be pink while the gastric mucosa was pale white color. The lesions on the mucosal wall demonstrated as long bands parallel to the axis of the stomach. Glandular areas displayed hyperemic and irregular lesions when compared to induction group, and treatment with famotidine inhibited the mucosal lesions induced by aspirin (ulcer index: 28.12). The ulcerative lesions in mice group given *c.papaya* seed extract were also prevented (ulcer index 39.67). We note that the glandular mucosa presented hyperemia due to Aspirin induced mucosal lesions, but hemorrhagic lesions were absent (Table 2).

Table 3: Gastric volume, PH, and gastric volume in experimental groups

Groups	Gastric volume (ml/100g)	Gastric pH	Acid output (Acidity) (mEq/L/100g)
Control	1.12±0.65	2.45±0.15	53.42±0.91
Aspirin	3.28±0.84*	1.10±0.93*	142.00±0.45*
Famotidine + Aspirin	1.43± 0.01$^{\#}$	2.08±0.92$^{\#}$	75.87±0.69$^{\#}$
c.papaya seed Extract +Aspirin	1.69±0.97$^{\#}$	1.99 ± 0.47$^{\#}$	77.39 ± 034$^{\#}$
*#: Statistically significant (p < 0.05) compared with Aspirin; *: Statistically significant (p < 0.05) compared with control*			

Aspirin administration caused a significant (p <0.05) reduction in PH as well as a significant (p <0.05) rise in stomach volume of gastric content, and increased acidity as compared to the control group. Prior administration of famotidine to mice as well as *c.papaya* seed extract caused significant reduction (p < 0.05) in gastric juice volume, and acidity, and a significant increase (p < 0.05) in gastric pH compared to animals given Aspirin. However, there was not statistically significant (p <0.05) difference when compared to the control group (Table 3).

Table 4: The oxidative stress levels in experimental groups

Group	MDA (umol/mg)	SOD (umol/mg)
Control	18.41 ±0.38	4.56±0.58
Aspirin	89.04 ± 0.29*	1.56 ±0.62*
Famotidine + Aspirin	27.31 ± 0.01$^{\#}$	3.91 ± 0.58$^{\#}$
c.papaya Extract +Aspirin	29.99 ±0.14$^{\#}$	4. 01 ±0.52$^{\#}$

#: Statistically significant (p < 0.05) compared with Aspirin; *: Statistically significant (p < 0.05) compared with control

Mice given aspirin exhibited significant rise (p < 0.05) in the level of malondialdehyde (MDA) and significant reduction (p < 0.05) in superoxide dismutase (SOD) activity when compared to control groups. Nevertheless, mice given famotidine and *c.papaya* seed extract displayed significant (p < 0.05) improvement in both MDA and SOD levels as compared to the aspirin group as shown in table 4.

Table 5: Proinflammatory cytokines (TNF) level in experimental animals

Group	TNF - (ng/ml)
Control	1.28 ± 0.04
Aspirin	3.56 ±0.15*
Famotidine + Aspirin	1.48 ± 0.27$^{\#}$
c.papaya Extract +Aspirin	1.39 ± 0.21$^{\#}$
*#: Statistically significant (p < 0.05) compared with Aspirin; *: Statistically significant (p < 0.05) compared with control*	

Mice given Aspirin significantly increased in serum level of tumor necrosis factor ($p < 0.05$) compared with control group, while both *c.papaya* seed extract and famotidine resulted in a significant ($p < 0.05$) improvement in the level of TNF as compared to the aspirin group as shown in table 5.

DISCUSSION

Peptic ulcer is a result of disproportion between the protective factors of gastric mucosa and the hostile destructive factors on the gastric wall. Herbal remedies and folkloric medicine have been used to aid in recovery and cure gastric mucosal walls [23]. It is a concrete fact that the use of non-steroidal anti-inflammatory medications like aspirin and its role in lipid peroxidation and generation of reactive oxygen species, as well as helicobacter pylori are the root cause of peptic ulcer [24].

The newly cultivated *carica papaya* plant seed extract was investigated in our study. Preliminary phytochemical analysis showed the presence of essential secondary active compounds like flavonoids, phenolic compounds which play a great role in the reducing oxidative stress, inflammatory mediators as generally described by literature as free radical – super oxide scavengers both directly and in directly [25], In addition alkaloids were present in the extract which matched research results. Carpaine, Pseudocarpaine, Dehydrocarpaine I and Il and Benzyl isothiocyanate (BITC) are some alkaloids mentioned in previous research that are present in papaya seed extract [26-28] these alkaloids are strong antioxidants and reported anti-inflammation properties all of which play a role in in preventing gastric ulcer [29]. Saponins were also found in the extract, previous research rarely mentioned saponins however its presence strongly contributes in gastric protection through enhanced gastric coating of mucus as well as its anti inflammatory effects [30, 31] Various phenolic acids such as caffeic and gallic acids were reported in previous research, tannins and flavonoids like rutin and quercetin are also identified. The latter phenolic classes all proved in literature to be antioxidants, in facts the presence on tannins can also contribute the astringency and gastric protection of papaya seed extract [32].

In our in-vitro model aspirin was used to induce the hemorrhagic necrotic lesions due to its role in altering the oxidant pathways leading to oxidative stress that highly contributes to gastric ulcer, and the C. papaya seed extract was shown to lessen this peptic laceration and producing a significant protection of gastric mucosa. This was revealed as the values of ulcer index were reduced when related to control group. The observed biochemical parameters were found to have significant increase in gastric volume, ulcer index, Acid output, pH, malondialdehyde (MDA) levels [33], and reduced SOD antioxidant activity after the administration of aspirin in the ulcerated induced mice. These results are parallel with the conclusion of Muhammad;' *et al.*, [34] and Sabiu *et al.*, [35]. The administration of Famotidine and the *c.papaya* seed extract rich in polyphenolic compounds and antioxidants retreated the aspirin induced peptic ulcer lesions. In addition, Proinflammatory cytokines (TNF) levels were measured and have significantly been lower as compared with control and aspirin induced experimental animals [36, 37].

CONCLUSION

carica papaya seed extract was assayed in our study it was reported in much research for its gastric protective properties due to its rich phytochemicals like polyphenolic compounds, phenolic acids, flavonoids, alkaloids and saponins as in the results. The in vitro results proved the gastroprotective effect of the seed extract in improving peptic ulcer condition. Future studies require isolation of compounds and investigation of further chemicals.

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