Quercetin and resveratrol effectson peptic ulcer in experimental rats

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Abstract: Generally, peptic ulcer disease is known as an inflammation or excavations in the mucous membrane and tissues of the gastrointestinal tract. Breakdown of the mucus membrane normally lining the esophagus, stomach and duodenum due to the action of gastric hydrochloric acid and pepsin usually leads to peptic ulcer lesions. Many synthetic anti-ulcer drugs (e.g., misoprostol) used for preventing or treating non-steroidal anti-inflammatory drugs (NSAIDs) made gastric lesions. On the other hand, such therapies can induce unpleasant side-effects like itching, skin rash, diarrhea, and dizziness. This study was designated to clear out the effect of quercetin, resveratrol and mixture of them on curing aspirin induced ulcers in male rats. Thirty-two male albino rats (200±10g b.wt.) were used and divided into 8 groups (n= 4 rats), one group was kept as control -ve group while rest of groups (7), were given orally aspirin (200mg/kg b.wt.) only (control +ve), while the rest of groups were treated orally with quercetin, resveratrol and mixture of them at two doses of 25 and 50 mg/kg b.wt., for each group for seven days. These parameteres were determined, gastric ulcer length, gastric juice volume, pH, total acidity and histopathological picture.It is concluded that oral treatment with both l quercetin and resveratrol at two dose levels (25 and 50 mg/kg b.wt.) shown significant reduction of gastric ulcerarea, total acidity, volume of gastric juice and histopathological changes. Moreover, quercetin extracts and resveratrol increased pH value of gastric juice. The rats administered with mixture of (quercetin + resveratrol) at dose of 50 mg/kg b.wt., showed the highest significant decrease in the gastric ulcer compared to all treated groups. Quercetin and resveratrol could be contribute in healing of gastric ulcer disease.

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Key words: Quercetin, resveratrol, peptic ulcer and histopathological changes.

1. Introduction

Breakdown in the mucous membrane in an area not less than 5mm in diameter is known as ulceration and occasionally happens due to disproportion between the luminal challenge exerted by the highly acidic and proteolytic properties of gastric juice and the ability of the mucous membranes to oppose it **(Hunt *et al*., 2015).** The site of ulcers in the GIT may be varied among Asian and European subjects. **Zhang and Haung, 2016** found in their study that the gastric ulcer represent 61.5%, while duodenal ulcers represent 32.8% in the studied patients. Other investigators reported that the duodenal ulcer was more predomoninant among Asian PUD patients (52.2%), and also reported that duodenal-ulcer may not changed to the malignant status. As a result, the survival rates among duodenal ulcer patients was better than that among gastric ulcer patients due to the tendency of gastric ulcers to be shifted to malignancy**.**

Plant kingdom are rich with naturally occurring compounds such as flavonoids which are a group secondary metabolites in fruits, vegetables, leaves and grains **(Goel and Bhattacharya, 1991).** Many researchers have been studied the therapeutic profits of quercetin and its derivatives on experimental animals as models of PUD. Due to their antioxidant and anti-inflammatory characteristics which are considered as a causative factors to therapeutic potency for peptic ulcers remedy. In addition, **Mohammad *et al*., 2015**, reported that quercetin, raises non-enzymatic and enzymatic antioxidant elements (protein sulfhydryl, superoxide dismutase (SOD), and catalase (CAT)). It corresponding lyconstrains neutrophil infiltration and the gastric tissue level of Myeloperoxidase (MPO)**.**

Resveratrol is another poly phenolic compound found in wine, nuts, red grapes and public garden plants, and which studied intensively among all phytochemicals due to its huge beneficial effects on human health. Resveratrol possessed many effects such as anti-oxidant and anti-aging characters, enhancement of insulin sensitivity and decrease in cardiovascular disease hazard. Another study **(Zixuan *et al*., 2017)** revealed that resveratrol have the capability to act as a chemo preventive and chemotherapeutic substance in some kinds of human cell carcinomas**.**

Therefore, this work aimed to study the impacts of quercetin, resveratrol and mixture of them on treating peptic ulcer induced by aspirin in rats.

2. Materials and Methods

1. Materials and rats:

1.1 Active ingredients:

The first active ingredient was quercetin dehydrate 95% which prepared as solid dispersion with polyvinyl pyrrolidone K30 to improve its solubility and the second was resveratrol (resveratrol (3,5,4′-trihydroxylstilbene).

1.2 Rats:

Male albino rats (200+10g b.wt., each) of Sprague Dawley Strain were purchased from King Fahd medical Research Center (KFMRC), Jeddah, KSA.

1.3 Drugs:

Ulcer agent (Aspirin) in form of ampule. Aspegic injection was prepared by dissolving one vial in 25ml distilled water to obtain solution. A volume of 1ml of this solution was orally given (at the level 200mg/kg body weight) for one day to induce acute gastric ulcer in male albino rats.

1.4 Basal Diet:

The basal diet (casein - basal diet) was composed of 12.3 g casein (10% protein), 10g corn oil (10% fat), 4 g minerals (4% minerals), 1g vitamin mixture (1% vitamin) 5 g cellulose (5% fiber) and corn starch up to 100g according to **Campbell (1961)**.

2. Methods:

2.1 Grouping design and feeding of rats:

The experiment was performed in Faculty of applied medical Sciences in Umm- Al-Qura. Rats were housed in wire cages in a room maintained at 25 + 2^{o}C and kept under normal healthy conditions. All rats were fed for one week on basal diet before starting the experiment for acclimatization. After one week period, rats were divided into two main groups. The first group (n= 4rats) was fed on the basal diet only as a control negative group (healthy rats). All rats in the second main group (n= 28 rats) were given orally aspirin at a dose of 200mg/kg b.wt., for induction of acute gastric ulcer according to **(Agrawal *et al.*, 2000).** Then, the second main group divided into 7groups as follow:

Group (2): Control positive group was fed on basal diet only.

Group (3): Was fed on basal diet plus oral feeding of quercetin at a single dose of 25mg/kg b.wt., for 7 days.

Group (4): Was fed on a basal diet plus oral feeding of quercetin at a single dose of 50 mg/kg b.wt., for 7 days.

Group (5): Was fed on a basal diet plus oral feeding of resveratrol at a single dose of 25 mg/kg b.wt., for 7 days.

Group (6): Was fed on a basal diet plus oral feeding of resveratrol at a single dose of 50 mg/kg b.wt., for 7 days.

Group (7): Was fed on a basal diet plus oral feeding of quercetin and resveratrol at a mix., dose of 25 mg/kg b.wt., for 7 days.

Group (8): Was fed on a basal diet plus oral feeding of quercetin and resveratrol at a mix., dose of 50 mg/kg b.wt., for 7 days.

2.2 Blood sampling:

At the end of the experimental period animals from each group were sacrificed and the blood was collected in a clean dry centrifuge tube, left at room temperature until the clot is formed, completely retracted and then centrifuged to separate serum by centrifugation at 4000 R.P.M., for 10minutes at room temperature followed by keeping in plastic vial (well stoppered) until analysis.

2.3 Measurement the length of gastric ulcer:

At the last day of experimental period, all rats were fasted for 12-14hrs and only allowed for drinking water. In the morning of the next day, all rats were sacrificed and their stomachs were tied around both openings (cardiac & pyloric sphincters) and injected with 3ml distilled water. The gastric juice was then collected in sterilized tube. The stomachs were opened longitudinally, washed with saline and examined under dissecting microscope for ulcer. The length of gastric ulcer was measured and expressed as mean+ standard deviation for each group. The curative ratio was then calculated for each treated group according to the method described by **Akhtar and Ahmad (1995)**.

2.4 Measurement the volume of gastric juice:

Gastric juice was collected in tubes and centrifuged at 500 R.P.M., for 5minutes. The volume of gastric juice was measured by graduated cylinder and expressed as ml.

2.5 Determination the total acidity and pH of gastric juice:

Total acidity was determined by titration of 1ml gastric juice in 10ml of distilled water with 0.01N NaOH using two drops of phenolphthalein as an indicator. Data were expressed as percentage. The pH degree was determined by pH meter.

2.6 Histopathological study:

Specimens from stomachs were collected from rats of all experimental groups at the end of the experimental period, fixed in 10% neutral buffered formalin (pH=7.0), dehydrated in ethyl alcohol, then cleared in xylol and embedded in paraffin; 4-6 microns thickness, sections prepared and stained with

haematoxylin and eosin for examining both fore and glandular parts of the stomach **(Carleton, 1976).**

2.7 Statistical analysis of data:

The obtained data were statistically analyzed using computerized SPSS (Statistic Program Sigmastat, statistical soft-ware, SAS Institute, Cary, NC). Effects of different treatments were analyzed by one way ANOVA (Analysis of variance) test using Duncan's multiple range test and $p<0.05$ was used to indicate significance between different groups **(Snedecor and Cochran, 1980).**

3. Results

1- Effect of quercetin and resveratrol on the gastric ulcer length in rats:

Results listed in table (1) illustrate the impact of quercetin and resveratrol and mixture of them at two doses in rats induced by aspirin.

Table (1): Effect of quercetin, resveratrol and mixture of them at two doses on the length of gastric ulcer in rats

Groups		Aspirin and Extracts	Doses (mg/kg B.wt.)	Gastric ulcer length (mm.) Mean ± SE
Control –ve	1	-	-	0.00
Control +ve	2	Aspirin (Asp)	200	6.98± 0.035 [a]
Treated Groups	3	(Asp) + Quercetin	25	4.05 ± 0.093 [c]
	4	(Asp) + Quercetin	50	2.93 ± 0.070 [f]
	5	(Asp) + Resveratrol	25	4.64 ± 0.041 [b]
	6	(Asp) + Resveratrol	50	3.89 ± 0.027 [d]
	7	(Asp) + Mix (Quercetin + Resveratrol)	25	3.17 ± 0.033 [e]
	8	(Asp) + Mix (Quercetin + Resveratrol)	50	2.01 ± 0.020 [g]

- Values denote arithmetic means ± standard error of the means
- Means with different letters (a, b, c, d) in the same column differ significantly at $p\leq0.05$using one way ANOVA test, while those with similar letters are non-significant.

t could be observed that the length of gastric ulcer in control +ve group was 6.98 ± 0.035 mm., compared with zero in control -ve group (normal rats). This mean that there were significant increase in gastric ulcer length in control positive group when compared to control negative one. All active ingredients quercetin 25 & 50 mg/kg b.wt, resveratrol 25 & 50 mg/kg b.wt., and Mix (quercetin + resveratrol) 25 & 50 mg/kg b.wt., showed significant decrease in gastric ulcer length as compared to control positive group which were 4.05 ± 0.093, 2.93 ± 0.070, 4.64 ± 0.041, 3.89 ± 0.027, 3.17 ± 0.033 and 2.01 ± 0.020 mm respectively. Rats administered with mix (quercetin + resveratrol) 50 mg/kg b.wt., showed the highest significant decrease in the length of gastric ulcer compared to all treated groups.

2- Effect of quercetin and resveratrol on volume of gastric juice in rats:

Table (2) show the effect of quercetin, resveratrol and mixture of them on the volume of gastric juice in rats.

Table (2): Effect of quercetin, resveratrol and mixture of them at two doses on volume of gastric juice in rats

Groups		Aspirin and Extracts	Doses (mg/kg b.wt.)	Volume of gastric juice (ml.) Mean ± SI
Control –ve	1	-	-	1.80 ± 0.007 [f]
Control +ve	2	Aspirin (Asp)	200	3.70 ± 0.087 [a]
Treated Groups	3	(Asp) + Quercetin	25	3.30 ± 0.023 [c]
	4	(Asp) + Quercetin	50	3.60 ± 0.048 [b]
	5	(Asp) + Resveratrol	25	2.30 ± 0.091 [e]
	6	(Asp) + Resveratrol	50	2.80 ± 0.029 [d]
	7	(Asp) + Mix (Quercetin + Resveratrol)	25	2.10 ± 0.018 [f]
	8	(Asp) + Mix (Quercetin + Resveratrol)	50	2.05 ± 0.026 [f]

- Values denote arithmetic means ± standard error of the means
- Means with different letters (a, b, c, d) in the same column differ significantly at $p\leq0.05$using one way ANOVA test, while those with similar letters are non-significant.

It is clear from table (2) that ulcerated rats in control positive group showed significant increase ($p\leq0.05$) in the volume of gastric juice in rats when compared to normal rats which were 3.70 ± 0.087 and

1.80± 0.007 ml respectively. All experimental groups which treated with quercetin, resveratrol and mixture of them showed significant decrease in the volume of gastric juice as compared to control positive group. Oral administration of (Asp) + mix (quercetin + resveratrol) at a dose of 50mg/kg, showed significant decrease ($p<0.05$) in the gastric juice volume in rats (2.05 ± 0.026 ml.) as compared with control positive group (3.70 ± 0.087 ml.).

3-Effect of quercetin and resveratrol on the pH of gastric juice in rats:

The effect of quercetin, resveratrol and mixture of them on the pH of gastric juice are shown in table (3).

Table (3): Effect of quercetin, resveratrol and mixture of them at two doses on pH of gastric juice in rats

Groups		Aspirin and Extracts	Doses (mg/kg b.wt.)	pH of gastric juice
				Mean ± SE
Control –ve	1	-	-	5.25 ± 0.036 [a]
Control +ve	2	Aspirin (Asp)	200	2.19 ± 0.022 [g]
Treated Groups	3	(Asp) + Quercetin	25	4.44 ± 0.083 [c]
	4	(Asp) + Quercetin	50	4.13 ± 0.039 [d]
	5	(Asp) + Resveratrol	25	3.82 ± 0.011 [f]
	6	(Asp) + Resveratrol	50	4.03 ± 0.071 [e]
	7	(Asp) + Mix (Quercetin + Resveratrol)	25	4.65 ± 0.046 [b]
	8	(Asp) + Mix (Quercetin + Resveratrol)	50	4.37 ± 0.094 [c]

- Values denote arithmetic means ± standard error of the means
- Means with different letters (a, b, c, d) in the same column differ significantly at $p\leq0.05$using one way ANOVA test, while those with similar letters are non-significant.

As shown in table (3) and figure (3), the result of this study found significant decrease in pH of gastric juice for rats in control +ve group, which orally administrated a dose of 200 mg/kg b.wt., of aspirin (2.19 ± 0.022 and 5.25 ± 0.036 respectively). Oral administration with quercetin at doses of 25 & 50mg/kg b.wt, resveratrol at doses of 25 & 50mg/kg b.wt., and mixture of quercetin and resveratrol at doses of 25 & 50 mg/kg b.wt., showed significant increase in the pH of gastric juice when compared to control positive group. Oral administration with the mixture of quercetin and resveratrol at a dose of 25 mg/kg b.wt., for each of them showed the highest significant increase in the pH of gastric juice in rats when compared to control positive group which were 4.65 ± 0.046 and 2.19 ± 0.022 respectively.

4. Effect of quercetin and resveratrol on the total acidity of gastric juice in rats:

The values in table (4) show the effect of quercetin, resveratrol and mixture of them at two dose levels on the gastric juice acidity in experimental rats.

Table (4): Effect of quercetin, resveratrol and mixture of them at two doses on the total acidity of gastric juice in rats

Groups		Aspirin and Extracts	Doses (mg/kg b.Wt.)	Total acidity (%)
				Mean ± SE
Control –ve	1	-	-	0.030± 0.002 [g]
Control +ve	2	Aspirin (Asp)	200	0.090± 0.009 [a]
Treated Groups	3	(Asp) + Quercetin	25	0.063± 0.003 [d]
	4	(Asp) + Quercetin	50	0.050± 0.008 [f]
	5	(Asp) + Resveratrol	25	0.055± 0.002 [e]
	6	(Asp) + Resveratrol	50	0.085± 0.008 [b]
	7	(Asp) + Mix (Quercetin + Resveratrol)	25	0.075± 0.001 [c]
	8	(Asp) + Mix (Quercetin + Resveratrol)	50	0.065± 0.003 [d]

- Values denote arithmetic means ± standard error of the means
- Means with different letters (a, b, c, d) in the same column differ significantly at $p\leq0.05$ using one way ANOVA test, while those with similar letters are non-significant.

It is clear from the results, that there were significant increase in the total acidity in gastric juice in rats in control +ve group compared to control –ve group which were 0.090± 0.009 and 0.030± 0.002 %, respectively. All groups of ulcerated rats which treated by quercetin, resveratrol and mixture of them at two

doses showed significant decrease in the percentage of the total acidity compared to control +ve +ve group. Oral treatment with 50 mg/kg quercetin showed the highest decrease in the percentage of total acidity in rats when compared to control positive group which were 0.050± 0.008 and 0.090± 0.009 %, respectively. Additionally, oral treatment with50 mg/kg b.w tresveratrol showed the lowest decline in total acidity of gastric juice compared to control positive group which were 0.085± 0.008 and 0.090 ± 0.009%, respectively.

5. Histopathological results

See Photos 1-8.

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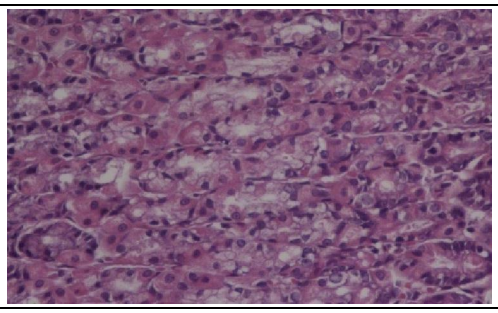
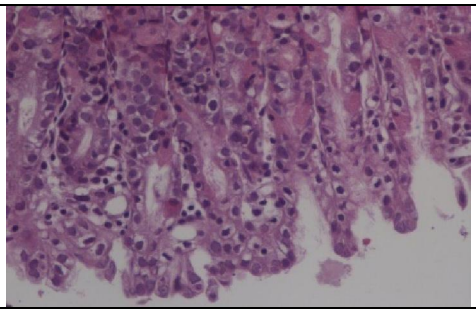
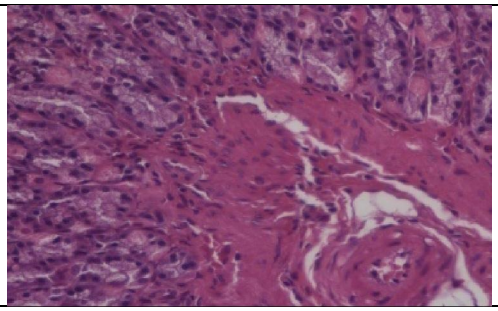
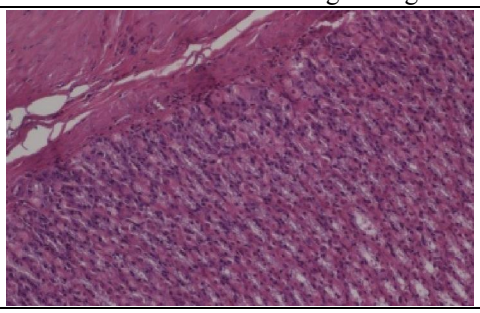
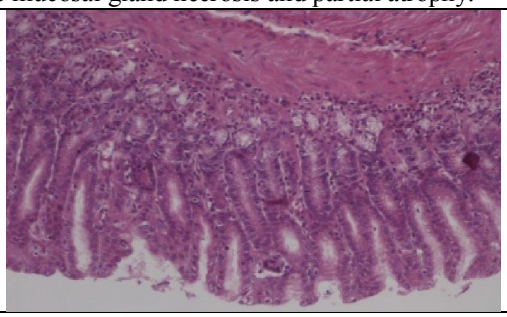
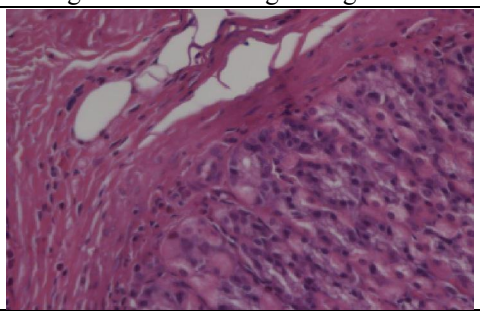
<tr><td>  </td><td>  </td></tr>
<tr><td>Photo (1): Rat stomach section from control negative group (Normal rats) showed normal mucosal gastric gland's.</td><td>Photo (2): Rat stomach section from control positive group showed hyperplastic mucosal layers of the stomach associated with necrosis of gastric glands.</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>Photo (3): Rat stomach section from group 3 (Quercetin at a dose of 25 mg/kg b.wt.) revealed little focal superficial gastric mucosal gland necrosis and partial atrophy.</td><td>Photo (4): Rat stomach section from group 4 (Quercetin at a dose of 50 mg/kg b.wt.) revealed gastro-esophageal wall showing normal mucosal gastric glands.</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>Photo (5): Rat stomach section from group 5 (Resveratrol at a dose of 25 mg/kg b.wt.) revealed partial atrophy of the mucosal glands.</td><td>Photo (6): Rat stomach section from group 6 (Resveratrol at a dose of 50 mg/kg b.wt.) revealed gastric wall with little focal superficial gastric mucosal gland necrosis.</td></tr>
</table>

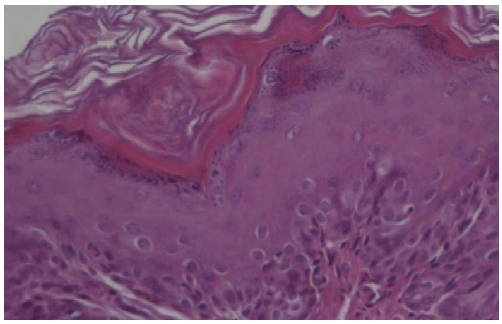
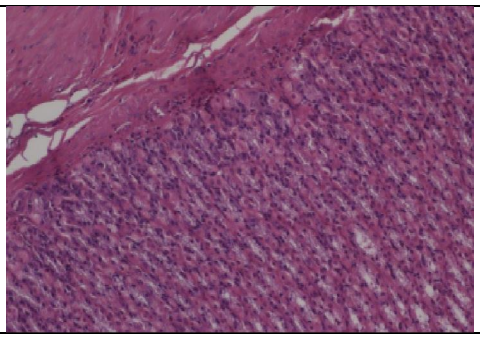
	

Photo (7): Rat stomach section from group 7 (Mixture of Quercetin and Resveratrol at a dose of 25 mg/kg b.wt.) revealed gastro-esophageal wall with lymphocytic cell infiltrate in the mucous.	Photo (8): Rat stomach section from group 8 (Mixture of Quercetin and Resveratrol at a dose of 50 mg/kg b.wt.) revealed gastro-esophageal wall showing normal mucosal gastric glands.

Discussion

The actual causes of peptic ulcer is not well defined but its considered as a multifactorial and complex disease which comprises both gastric and duodenal ulcers. Many synthetic anti-ulcer drugs (e.g., misoprostol) used for preventing or treating non-steroidal anti-inflammatory drugs (NSAIDs) induced gastric ulcers.

Hence, there is a changed awareness toward medicinal plant extracts as a source of non-toxic and natural anti-ulcer formulations from these plants. One of the most secondary metabolite groups are flavonoids which are a naturally-founding group of composites. Quercetin is one of the flavonoids, which has been found to possess antioxidant activity and thus, can suppress damage to the cells as a result of oxidant radicals and prevent the death of cells. Quercetin is extensively found in fruits and vegetables such as apples, berries, onions, and tea.

Resveratrol is another poly phenolic compound found with sufficient quantities in nuts, red grapes, and public garden plants, and is paid great attention rather than any of all studied phytochemicals due to it is as sumeduseful actions on human health.

In the present study, Ulcerated rats which treated with quercetin at doses of 25 & 50 mg/kg B.wt., showed significant decrease in gastric ulcer length as compared to control positive group which were 4.05 ± 0.093, 2.93 ± 0.070mm respectively. This result was in agreement with **(Abdullah and Naser, 2016)** who revealed that the rats treated with 50 mg/kg b.wt. quercetin, demonstrated an ulcer index of 19.55+0.62 mm, which is significantly ($p<0.05$) less than that obtained after treatment with standard anti-inflammatory drug (indomethacin) treated groups. Therefore, it is evident that the treatment of experimental animals with quercetin resulted in additional efficient protection against induction of gastric ulcers in comparison with famotidine therapy.

Ahmet *et al.* (2003) reported that treated with quercetin followed by administration of ethanol (for induction of gastric ulcers), the results revealed to a significant inhibition in the formation of mucous membrane ulcers in the stomach of rats given ethyl alcohol for induction of ulcers. Quercetin treatment was found to decreased significantly the number of mast cells and decrease the area of mucosal gastric damage. This finding coordinate with our data which cleared that treatment with 25 and 50 mg/kg body weight quercetin, significantly reduced the length of gastric ulcer.

Other study concluded that resveratrol carry protective effects against *H. pylori* associated gastritis by inducing antioxidant activity against oxidative stress or free radicals and also inducing anti-inflammatory action through different mechanisms: 1. inhibiting the levels of expression of IL-8 and iNOS; 2. hindering the activation of NF-B, and 3. increasing the expression levels of the Nrf2 and HO-1 in *H. pylori*-infected mucosal layer in the stomach. In addition, resveratrol could be supplemented to the food in order to protect the gastric mucosa from *H. pylori*-associated gastritis and diminish the incidence of gastric cancer in humans **(Xiaolin*et al.*, 2015).** These results agreed with the result of the present study which reported in +ve control group that the average length of gastric ulcer was 6.98 ± 0.035 mm, as compared with normal rats (–ve control) which reached zero value. This means that there was significant increase in gastric ulcer length in control positive group when compared to control negative one. All ulcerated rats which treated with resveratrol at doses of 25 & 50 mg/kg b.wt., showed significant decrease in gastric ulcer length as compared to control positive group which were 4.64 ± 0.041 and 3.89 ± 0.027 mm respectively.

The pathogenesis of *H. pylori* infection was hypothesized as stimulation of the pro-inflammatory mediators, leading to disorder of surface epithelial cell

reliability, irregularity of the luminal margin, impairment in the gastric microvilli, and causing mucosal vacuolation. Interleukin-8(IL-8) is one of the proinflammatory cytokines which play an important role in the *H. pylori* disease pathogenesis, through stimulating neutrophilic cells and bringing cellular chemo-attraction. The mode of action of resveratrol was illustrated by **Zaidi*et al.* (2009)**, they reported that resveratrol can stop the damage in the mucous membrane of the stomach resulted from gastritis induced by *H.pylori* infection via inhibiting the secretion and/or expression of IL-8 from the mucosal cells infected with *H.pylori*. This finding is nearly coordinated with our findings which reported a significant reduction in gastric ulcer length.

Some researchers reported that oral pretreatment of rats with 100 mg.kg quercetin, 30 min before surgical cession decreased significantly the lesion length in the gastric mucosa. Conversely, administration of low doses (25 and 50 mg.kg) of quercetin had slight effect on the healing of gastric mucosal lesion **(Mojzis *et al.*, 2001).** This result is agreed with present results which showed significant decrease in gastric ulcer length.

Oral administration of 50mg/kg b.wt., (Asp) + mix (quercetin + resveratrol) resulted in a high reduction in the volume of gastric juice (2.05 ± 0.026 ml. vs. 3.70 ± 0.087 ml.) in treated rats. This result is nearly agreed with **(Min *et al.*,2009)** which reported that quercetin prevents indomethacin-induced gastric ulcer dose-dependency *via* the reduction of gastric volumes.

It is clear from the results that ulcerated rats in control positive group showed significant increase ($p \leq 0.05$) in the volume of gastric juice when compared to Control –ve group which were 3.70 ± 0.087ml and 1.80± 0.007 ml respectively. All experimental groups of rats which treated with a dose of 25 & 50 mg/kg b.wt, quercetin showed significant reduction in the volume of gastric juice in comparison with control positive group. These result were agreed with **(Abdullah and Naser, 2016)** who studied the protective effect of quercetin on gastric ulcer, they found that in rats treated with indomethacin (+ve group), the volume of gastric juice was considerably higher (0.8 ±0.14 ml) than that in normal control rats (0.26±0.05 ml). Relatively, in rats treated with indomethacin and was given also quercetin, the volume of gastric juice did not show any increase with regard to control group (0.22±0.15 vs. 0.30±0.42).

Shakeerabanu *et al.* (2011) reported that treatment of ulcerated rats with quercetin was associated with lowering in acidity and low release of acid and pepsin concentration, which are necessary for rapid healing of gastric ulcers and protection against ulcer formation. This result agree with our result which found that oral giving of quercetin at two dose levels (25 and 50 mg/kg) showed the maximum decrease in percentage of total acidity in rats (0.063± 0.003 and 0.050± 0.008 respectively) when compared to control positive group (0.090± 0.009).

Other authors **(Min *et al.*, 2009)** recorded that quercetin-3-O-β-D-glucuronopyranoside suppresses indomethacin-induced gastric ulcer dose-dependency. It reduces gastric acid secretion through the reduction of total acidity. This result is parallel with other study in which quercetin was given at two dose levels (25 and 50 mg/kg b.wt.) they found a highly reduction in the percentage of total acidity in treated rats rather than control positive group (0.063± 0.003 and 0.050± 0.008 Vs. 0.090± 0.009 %, respectively).

Shakeerabanu *et al.* (2011) found increasing in pH and decreasing in acidity, acid output and pepsin concentration were proved in ulcerated animals treated with quercetin, which is preferred in case of gastroenteritis, where it found to protect the mucosal layers from damage and acting as antiulcerative agent. Also **(Abdullah and Naser, 2016)** concluded a reduction in the pH of gastric juice (3.07±0.58) in indomethacin-treated rats in comparison with normal rats (pH, 4.57±0.24) though, treatment of indomethacin-treated rats with quercetin resulted in decrease in pH values similar to that of the controls. The pH values of those rats who received famotidine were even less acidic (5.52±0.21). The present study reported that oral administration of quercetin at 25 and 50mg/kg b.wt., of rats significant increase pH of gastric juice. Moreover oral administration of quercetin at a dose of 50 mg/kg body weight showed the highest significant decrease in the percentage of total acidity in rats when compared to control positive group which were 0.050± 0.008 and 0.090± 0.009% respectively.

While**, Brown and Jiang (2012)** found that there was not much effect of changes in pH over the range examined with either strain or any of the compound concentrations tested. At 4o the MIC, H. pylori populations were reduced almost three logs within 6 hours by quercetin and resveratrol at PH 7.4 and within 24 hours at PH 5.8.

Xiaolin *et al.* (2015) studied the Effect of resveratrol on H. pylori-Caused Gastric Tissue Inflammation, They found that the gastric mucosal tissue of resveratrol-treated animals exhibited obvious improvement of inflammatory cell infiltration. The results of histological grading suggest that resveratrol antagonizes H. pylori-induced gastric inflammation and improves the histopathological grade of gastritis in ‘mouse stomachs. This result was agreed with the present histopathological results which showed that the rat stomach section from group that received resveratrol at a dose of 25 mg/kg b.wt. revealed partial

atrophy of the mucosal glands, and group that received a dose of 50 mg/kg b.wt. revealed gastric wall with little focal superficial gastric mucosal gland necrosis.

Conclusion

In conclusion, all ulcerated rats treated with quercetin and resveratrol at doses of 25 & 50 mg/kg b.Wt, showed significant increase in the pH of gastric juice and significant decrease in gastric ulcer (length, volume and acidity).The rats administered with mixture of (quercetin + resveratrol) at dose of 50 mg/kg b.wt., showed the highest significant decrease in the gastric ulcer compared to all treated groups.

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