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RESEARCH ARTICLE

THE POSSIBLE EFFECTS OF *THYMOQUINONE* AND PARSLEY IN EXPERIMENTALLY INDUCED RENAL INJURY ASSOCIATED WITH GASTRIC ULCER IN RATS

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Abstract

Acute renal failure (ARF) is still associated with high in-hospital mortality, may be due to acute gastrointestinal hemorrhage (AGIH), especially in the upper gastrointestinal tract. Gastric ulcers and/or erosions are the most common source of AGIH. Objective: This study investigates the effect of thymoquinone (TQ) and parsley in experimentally induced renal injury associated with gastric ulcer. Materials and methods: A total of 80 rats were randomly classified into four experimental groups: Group 1 (normal group), Group 2 (Gly & ethanol) for induction of renal injury and ulcer, group 3 and 4 receive thymoquinone (10 mg/kg) and parsley (600 mg/kg) respectively for 14 days. The serum levels of creatinine, blood urea nitrogen (BUN) and potassium were measured. Malodialdehyde (TBARs) and reduced glutathione (GSH), myeloperoxidase (MPO), tumour necrosis factor alpha (TNF-α), caspase 3 activity and superoxide dismutase (SOD) activities were measured in stomach and renal tissue, also gastric mucosal lesions and ulcer index were assessed. Renal and stomach histopathological examination were carried out. Results: Glycerol and ethanol caused renal and gastric injury noted by increased level of creatinine, BUN, TBARs, MPO, TNFα, caspase 3 activity and decrease GSH content, SOD activity, Histopathological examination revealed definite alterations. Thymoquinone and parsley significantly reduced serum creatinine, BUN, potassium, TBARs, MPO, TNFα, caspase 3 activity, gastric ulcer, gastric index as well as histopathlogical examination and significantly increased GSH content and SOD activity. Conclusion: based on our study it could be concluded that TQ and parsley have protective effects in renal injury associated with gastric ulcer.

INTRODUCTION

Acute renal failure (ARF) is still associated with high in-hospital mortality **(Star, 1998)**, may be due to acute gastrointestinal hemorrhage (AGIH), especially in the upper gastrointestinal tract. **(Frost *et al.*, 1993; Klouche *et al.*, 1995)**

Renal insufficiency has been shown to be a predictor of mortality in previously validated upper GI bleeding scoring systems, such as the Rockall score **(Rockall *et al.*, 1996)**, peptic ulcer bleeding appears to be the most common cause of acute upper GI bleeding seen in CKD **(Chalasani *et al.*, 1996)**.

Gastric ulcers and/or erosions are the most common source of AGIH. Stress-related mucosal injury in the critically ill is thought to originate from a complex interplay of aggressive luminal factors (normal or increased acid secretion) and altered gastric mucosa defense mechanisms (reduced mucosal blood flow, mucosal barrier disruption, decreased mucus, and prostaglandin production, etc.) **(Zuckerman *et al.*, 1988)**.

Thymoquinone is extracted from the oil of Nigella sativa **(Burits and Bucar, 2000)**, and in recent studies it has been reported to be immunomodulatory **(Chakravarty, 1993)**, anti-inflammatory **(Ghannadi *et al.*, 2005)**, antitumor **(Badary and Gamal El-Din, 2001)**, antidiabetic **(Abdelmeguid *et al.*, 2010)**,and antinociceptive **(Abdel-Fattah *et al.*, 2000)**. It was found that the administration of TQ led to decreased malondialdehyde (MDA) levels **(Alenzi *et al.*, 2010)**, TNF- α production **(El Gazzar *et al.*, 2007)**, antihistaminic, antibacterial, antihypertensive, hypoglycemic, anti-inflammatory, immunopotentiating **(Ahmad and Beg, 2013).**

Parsley (*Petroselinum crispum*, family Umbelliferae) is used for flushing the efferent urinary tract, as a diuretic **(Kreydiyyeh and Usta, 2002)** and for the prevention and treatment of kidney gravel. In folk medicine of many countries, it is used for gastrointestinal disorders **(Kreydiyyeh *et al.*, 2001)** and to cure jaundice. The leaves and seeds of this plant are used for the treatment of diarrhea, stomachache, indigestion, dropsy, menstrual difficulties and to treat gallstones , stimulate appetite and treat flatulence **(Al-Howiriny *et al.*, 2003)**.

The aim of the present study was to investigate the effect of thymoquinone and parsley on renal injury associated with gastric ulcer in rats

Materials and methods

Animals

Adult male Sprague-Dawley rats weighing 190-250 g will be used in the present study. Study carried out according to the approval of ethics committee for animal's experimentation at faculty of pharmacy, Cairo University.

The animals will be housed in the animal facility of Faculty of Pharmacy, Egyptian Russian University. They were fed with standard diet pellets (El-Nasr Company, Abou-Zaabal, Cairo, Egypt), and allowed free access to water. The rats were kept under standard conditions of temperature (21°C ± 0.5) and relative humidity (55 ± 1) with 12-light/12-dark cycle.

Drugs

Thymoquinone and parsley was purchased from Sigma-Aldrich (St. Louis, MO).

Glycerol and ethanol was purchased from Elgomheria Company, Giza, Egypt

Experimental design

Rats were randomly allocated into 4 groups (20 rats each) as follows:

Group 1: Rats served as normal group (receiving Saline)

Group 2: Received Gly solution (50%, v/v in sterile saline, I.M in a dose of 8 ml/kg **(Vlahovic *et al.*, 2007)**. Animals were allowed free access to food but deprived of drinking water for 24 h before the Gly injection. The injected volume was divided equally between the two hind limbs. And oral administration 1 ml ethanol one hour before end of experiment **(Perez Guerrero *et al.*, 1994)**

Group 3: Treated exactly as group 2, but received thymoquinone (10 mg/kg) orally/day **(Fouda *et al.*, 2008; Padhye *et al.*, 2008)** 12 days prior to the Gly injection. The dose was repeated once every 24 h for another two consecutive days.

Group 4: Treated as group 2, but received parsley (600 mg/kg) **(Saeidi *et al.*, 2012; Fahmy *et al.*, 2014)** orally/day 12 days prior to the Gly injection. The dose was repeated once every 24 h for another two consecutive days.

Blood samples will be withdrawn via retro-orbital plexus under light anesthesia diethyl ether. After then, rats will be sacrificed by cervical dislocation; their stomachs and kidneys will be excised for further evaluation.

Gastric mucosal lesions will be evaluated by visual scores for the severity and number of lesions/rat.**(Pendley *et al.*, 1993; Li *et al.*, 1998)**

Stomach and kidneys were isolated immediately and fixed in 10% buffered formalin for histopathological examination. One kidney from 7 rats used for histopathological examination and the remaining homogenized and used for biochemical parameters. The used dead bodies will be frozen at -20C till being incinerated.

Biochemical assay

The serum levels of creatinine, blood urea nitrogen and potassium were measured using kits supplied by Biodiagnostic, Egypt

TBARs , GSH content and nitrite content as well as SOD activity in stomach and renal tissue were determined spectrophotometrically using commercial kits supplied by Biodiagnostic, Egypt.

Caspase 3 was determined according to ELISA Kit (Uscn Life Science Inc. Wuhan.)

Gastric and renal tissue content of TNF-α and myeloperoxidase (MPO) were measured by ELISA (AssayPro and Hycult Biotechnology, USA respectively).

Histopathological examination

Kidney and stomach specimens from all animals were stained with Haematoxylin and eosin for histopathological investigation **(Carleton *et al*., 1980).**

Statistical analysis

All data were statistically analyzed by one-way analysis of variance (ANOVA), followed by Tukey-Kramer multiple comparisons test. A probability of less than 0.05 was accepted as being significant in all types of statistical tests. Instat software, version 3 (Graphpad software, Inc., San Diego, USA) was used to carry out all the statistical tests in the present study. The values were expressed as mean ± standard error (S.E)

Results

Effect of Thymoquinone and Parsley on serum creatinine, creatinine clearance, blood urea nitrogen, urine volume and kidney weight / body weight ratio in glycerol - induced acute renal failure associated with gastric ulcer in rats.

There was significant increase in creatinine, BUN, urine volume and kidney weight / body weight ration by 346%,194%, 460%, 121% respectively and decrease in creatinine clearance by 61% in group 2 compared to group1. Administration of thymoquinone markedly decreases creatinine, BUN, urine volume and kidney weight / body weight ration by 26%, 34%, 34% and 47% respectively and increase creatinine clearance by43 % as compared to group 2. While administration of parsley markedly decreases creatinine, BUN, urine volume and kidney weight / body weight ration by 32%, 39%, 55% and 48% respectively and increase creatinine clearance by 43 % as compared to group 2 (**Table 1).**

Effect of Thymoquinone and Parsley on serum potassium and urine total protein in glycerol induced acute renal failure associated with gastric ulcer in rats.

Compared with findings in the group 1, the serum levels of potassium and urine total protein were significantly increased in the group 2 by 59% and 488% respectively,

This increase was significantly decreased in group 3 by 20% and 29% respectively when compared with group 2. Corresponding findings were found for group 4 (26% and 41% respectively) as compared to group 2 (**Table 2).**

Effect of Thymoquinone and Parsley on super oxide dismutase, glutathione content, thiobarbituric acid reactive substances, Myeloperoxidase enzyme activity and Nitrite concentration in glycerol induced acute renal failure associated with gastric ulcer in rats.

Treatment with glycerol and ethanol significantly decreased the enzymatic activity of superoxide dismutase and GSH content in kidney and stomach by 52%, 63% 59% and 67% respectively as compared to group 1(Fig1 a, b ,c,d respectively) and significantly increased TBARS, MPO and nitrite content in the kidney by 189%, 940%, 85% respectively (fig 1 e, g ,I respectively) and stomach tissue by 823%, 259%, 422% respectively as compared to group 1. (Fig 1 f, h, j respectively)

Pretreatment of thymoquinone modulate the decreased SOD in kidney and stomach by 57%, 174 % respectively (Fig1 a, b respectively) as well as GSH content (112% and 162% respectively) (Fig1 c, d respectively) and modulate the increased TBARS, MPO and nitrite content in the kidney by 27%, 32%, 24% respectively (fig 1 e ,g, I respectively), and stomach by 70%, 32%, 43% respectively as compared to group 2 (Fig 1 f, h, j respectively).

Parsley modulate the decreased SOD in kidney and stomach by 41% ,85% respectively (Fig1 a,b respectively) as well as GSH content (154% and 353% respectively)) (Fig1 c , d respectively) and modulate the increased TBARS,MPO and nitrite content in the kidney by 27%, 32%, 24% respectively(fig 1 e, g ,I respectively), and Stomach by 29%, 32%, 43%, respectively as compared to group 2 (Fig 1 f, h, j respectively).

Effect of Thymoquinone and Parsley on tumor necrosis factor alpha and caspase 3 activity in glycerol - induced acute renal failure associated with gastric ulcer in rats.

There was significant increase in TNF α and Caspase 3 activity in group 2 as Compared to group1. Administration of thymoquinone and or parsley markedly decreases TNF α and Caspase 3 activity as compared to group 2. (Fig 2 a, b, c, d respectively)

Effect of Thymoquinone and Parsley on ulcer number and ulcer index in glycerol - induced acute renal failure associated with gastric ulcer in rats.

There was significant increase in ulcer number and ulcer index in group 2(45.57 ± 2.09 and 97.29 ± 4.77) respectively. Administration of Thymoquinone and Parsley markedly decreases ulcer number and ulcer index as compared to group 2.(16.00 ± 1.36 and 30.63± 1.99 respectively as regardes to TQ) and (17.60 ± 0.81 and $35.38^{@}$ ± 2.50 respectively as regardes to parsley) (Table 3).

Histopathological studies

Rats shows hemorrhage beneath the gastric pits (arrow) with atrophy of the surface mucous secreting cells (arrowhead) and loss of the entire mucosa (group 2 fig 3c). Renal tissue shows severe damage of all elements, suffering from vacuolar degeneration of their lining cells (arrow) or atrophy with widening of their lumen (arrowhead), interstitial hemorrhage (H) (group 2 fig 3d). Rats show tissue amelioration of the structural changes, although there are multiple small gaps (group 3 fig 3E). And shows in renal tissue many tubules regain their normal lining epithelium, although their lumen were widened (arrow), the glomeruli (G) are more or less normal (group 3 **fig** 3F).

Rats shows quite normal gastric mucosal tissue, however, there are small gaps in the glands due to atrophy of some cells (arrow) and fine hemorrhage in between the surface mucous secreting cells (black arrowhead), there is widening of the gastric pits (green arrowhead) (group 4 fig 3G). Normal tissue shows normal glomeruli. Most of the tubules appear close to normal (arrowhead), a few tubules show damage signs (arrow) (group 4 fig 3H)

Discussion

The present study, we investigated the possible protective effect of thymoquinone and parsley against glycerol induced nephrotoxicity and ethanol induced gastric ulcer.

Previous data postulates that glycerol injection promotes the formation of a variety of vasoconstrictors leading to renal vasoconstriction that may reduce renal blood flow and glomerular filtration rate affecting renal function leading to renal damage **(Nath *et al.*, 1992)**. On the basis of this mechanism and that creatinine passes out in urine only through the kidney, so when kidneys are damaged and GFR is reduced, its level in urine is decreased **(Park *et al.*, 2012)**And since revealed a significant decrease in creatinine clearance following glycerol administration, so consequently Urine Cr will be reduced.

In the present study, pretreatment with TQ or parsley decrease S cr , BUN, urine volume, Kw/Bw , serum potassium, UTP and increase Cr cl. Similar results have been reported by **(Badary *et al.*, 2000; Vlahovic *et al.*, 2007; Basarslan *et al.*, 2012; Elsherbiny and El-Sherbiny, 2014)**. Also TQ modulate the decreased SOD activity, GSH content **(El-Abhar *et al.*, 2003; Fouda *et al.*, 2008; Randhawa *et al.*, 2013)** and decrease TBARs content **(Basarslan *et al.*, 2012; Randhawa *et al.*, 2013)**, MPO activity **(Fayez *et al.*, 2014)**, nitrite content **(Sedaghat *et al.*, 2014)**, TNF α **(Fouda *et al.*, 2008; Umar *et al.*, 2012)** and caspase 3 activities **(Fayez *et al.*, 2014)** in kidney and stomach. The present data are in agreement with previous study.

Thymoquinone acts as a potent scavenger of superoxide, hydroxyl radical and singlet molecular oxygen **(Kruk *et al.*, 2000)**, inhibiting iron-dependent microsomal lipid peroxidation **(Badary *et al.*, 2003)**, possess antioxidant **(Kruk *et al.*, 2000; Nagi and Mansour, 2000)**, anti-inflammatory **(Houghton *et al.*, 1995; Al-Ghamdi, 2001)**.

Previous studies have shown that pre-treatment with thymoquinone protected organs against oxidative damage induced by a variety of free radical generating agents, including cisplatin **(Badary *et al.*, 1997)**, carbon tetrachloride **(Mansour, 2000)** and doxorubicin **(Nagi and Mansour, 2000)** Moreover, thymoquinone supplementation has recently been shown to prevent deterioration of the biochemical and histological indices

of gentamicin-induced nephrotoxicity, which is coincide with the increase in the total antioxidant status in renal cortex, including GSH concentration.**(Verstrepen *et al.*, 1995)**. The strong antioxidant potentials of thymoquinone may be related to the redox properties of the quinone structure of thymoquinone molecule and its unrestricted crossing of morphophysiological barriers, and easy access to subcellular compartments facilitates the ROS scavenging effect **(Brunmark *et al.*, 1988; Daba and Abdel-Rahman, 1998)**.

Thymoquinone administration in this study reduced apoptosis through decreasing the activation of caspase-3. This is in agreement with **(Fouda *et al.*, 2008)** who reported that apoptosis and proliferative reactions are reduced by thymoquinone. Also **Kanter *et al* (2005)** reported that oral administration of TQ at a dose of 10 mg/kg orally protected the animals against alcohol-induced ulcers by via antioxidant mechanisms that involved inhibition of reactive oxygen radicals and an increase in superoxide dismutase availability.

Thymoquinone showed a marked improve in the renal and gastric cells structure. These results are in agreement with that of many studies that have shown a protective role of TQ **(Hosseinzadeh *et al.*, 2007; Newairy *et al.*, 2009)**.

The rapid improvement of these cellular defense enzymes may be partially due to prevention by thymoquinone of the rapid depletion of intracellular GSH **(Daba and Abdel-Rahman, 1998)** either by acting as a shield against free radical attacks, or by stimulating the early regeneration of these antioxidant enzymes as well as its ability to prevent the energy decline in kidney tissues **(Sayed-Ahmed and Nagi, 2007)**. Thymoquinone has been recently shown to inhibit TNF-α production in rat model of rheumatoid arthritis **(Tekeoglu *et al.*, 2006)**.

In the present study, we found that parsley protective in both kidney and stomach tissue. The protective effect of the Parsley can be achieved through increased mucus secretion that will reinforce gastric mucus defenses, strengthening the gastric mucus-bicarbonate **(Wallace and Whittle, 1986; Alvarez *et al.*, 1999)**. Or through the reduction of proteolytic activity of the pepsin in the gastric juice. There is mounting evidence that suppressants of gastric acid secretion are known to increase the healing of both human and experimental gastric ulcers **(Olsen *et al.*, 1986; Kang *et al.*, 1996)**. The enhanced gastric NP-SH and mucus levels may contribute to Parsley antiulcer activity **(Rafatullah *et al.*, 1995)**.

Parsley extract has been shown to protect gastric lesions induced by noxious chemicals (ethanol) these agents are known as to promote oxygen free radicals **(Szelenyi and Brune, 1988; Halliwell, 1991)**, reduced gastric mucosal non-protein sulfhydryl levels **(Szabo *et al.*, 1981)** and stimulate the formation of leukoterine C4 (LTC4), a lipoxygenase derived metabolite of arachidonic acid **(Hua *et al.*, 1985)**. Constriction of submucosal venules with subsequent stasis of blood flow in mucosal microcirculation as well as plasma leakage from the vascular bed can contribute to the widespread mucosal injury **(Trier *et al.*, 1987)**.

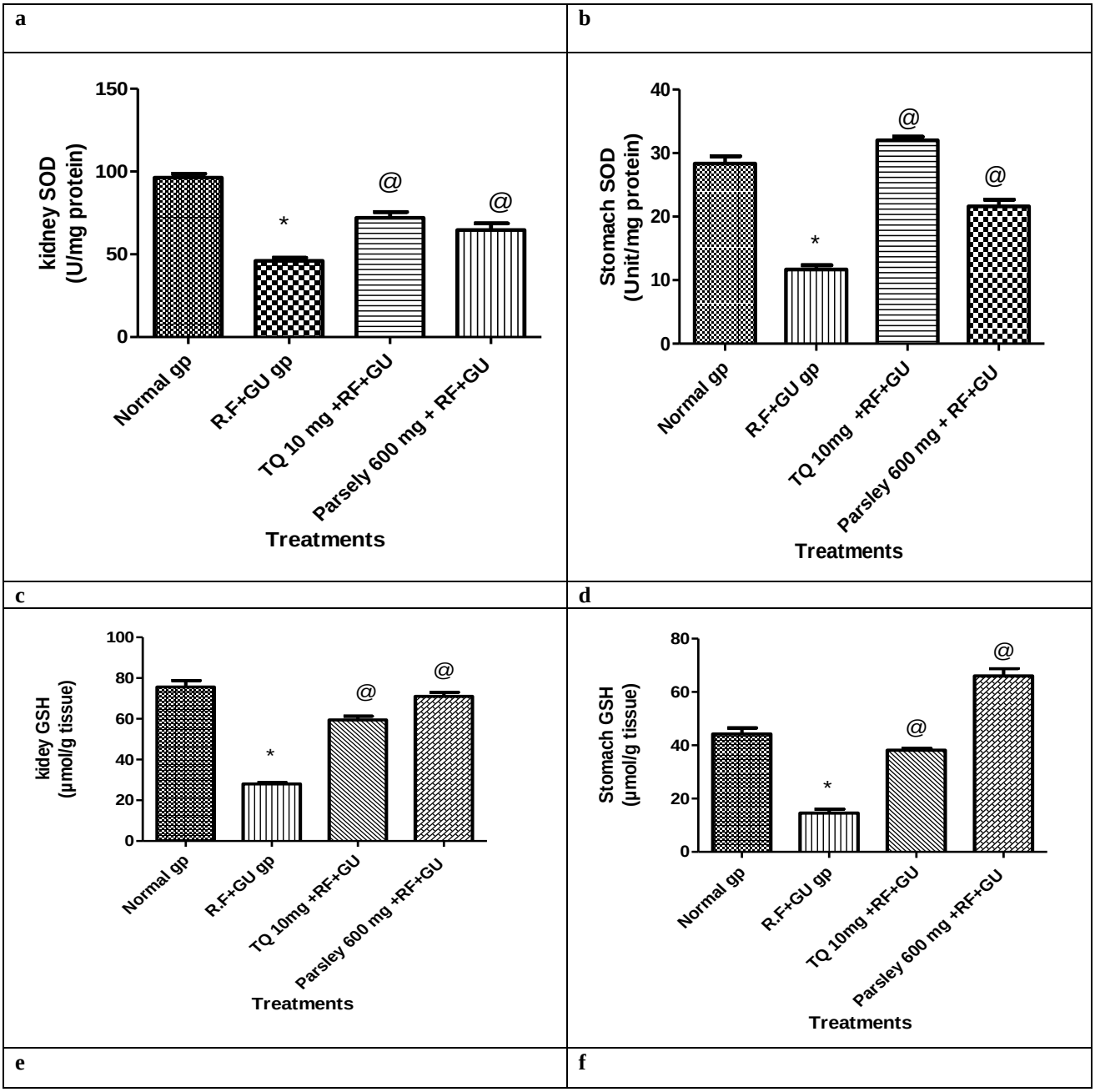
The results on histopathological investigation on the gastric mucosa of rats revealed the pretreatment with TQ and Parsley absolutely inhibited the ethanol-induced congestion, hemorrhage, edema, necrosis, inflammatory and dysplastic changes, erosions and ulceration. Our results are in corroboration with the anti-gastric ulcer activity of the extract observed under the studies on pharmacological and biochemical evaluation.

In conclusion parsley was considered as good protector for kidney and stomach due to its antioxidant power as good sources of phenolic compounds (Antioxidant activity).**(Ozsoy-Sacan *et al.*, 2006; Abdel-Rahim and El-Beltagi, 2010)**. this vegetable contains many natural compounds such as protein, fiber, vitamin A, high concentration of β-carotene, vitamin C both had good power as Antioxidant **(Pattison *et al.*, 2004)** and folic acid as well as several phenolic compounds such as catechin, phenol, daidzin, *P*-coumaric, genistein, ferulic, querctin, chrysin and galangin and others.

Abdel-Rahim and El-Beltagi (2010) found that pretreatment with parsley showed significant improvements in the kidneys function. **Lin *et al* (2005)** reported that antioxidative compounds role is most respect among all other protective factors. In another wards, feeding systems containing a particular substance is vital, a single nutrient may not work alone. This may suggests that the oxidant defense mechanisms in which these antioxidant nutrients function are sometimes independent of one another despite fighting in different areas **(Burk *et al.*, 2008)**.

In Conclusion

We found that Thymoquinone and Parsley are protective against gastric and renal injury due to their antioxidant activity and the capacity to scavenge free radicals.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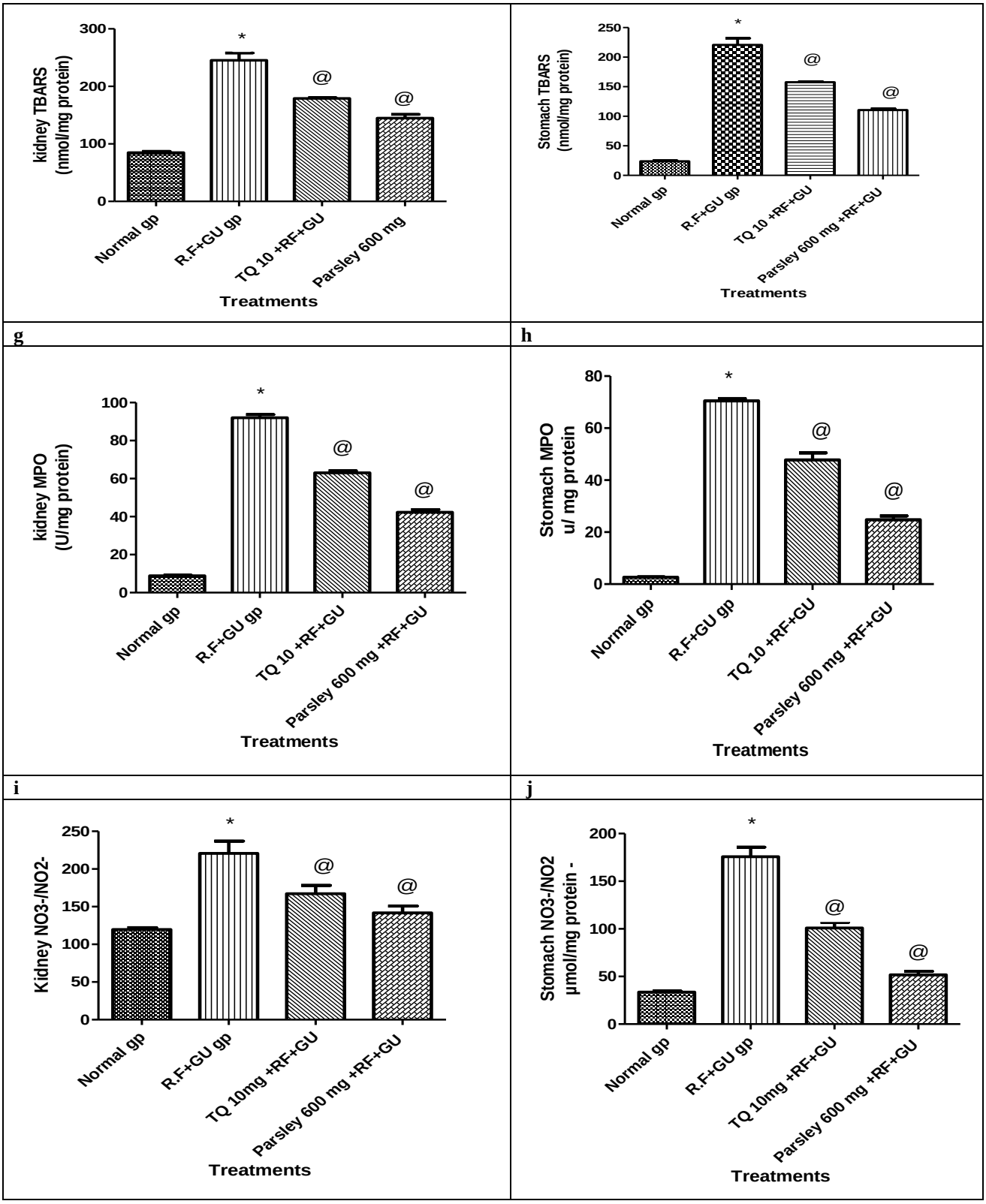

Fig 1 (a-j): Effect of Thymoquinone and Parsley on superoxide dismutase, glutathione content, thiobarbituric acid reactive substances , Myeloperoxidase enzyme activity and Nitrite concentration in glycerol and ethanol - induced acute renal failure with gastric ulcer in rats.
(Group 1): Normal group (receiving Saline)

(Group 2): R.F + G.U group receiving Gly (8 ml/kg) +Ethanol (1ml/rat))
(Group 3): Group receiving thymoquinone (10 mg/kg), Gly (8 ml/kg) and Ethanol (1ml/rat)
(Group 4): Group receiving parsley (600 mg/kg), Gly (8 ml/kg) and Ethanol (1ml/rat)
Values are means of samples ± SEM. (n=9)
* Significant change compared with the normal group at $p<0.05$
@Significant change compared with R.F and G.U. group at $p<0.05$.

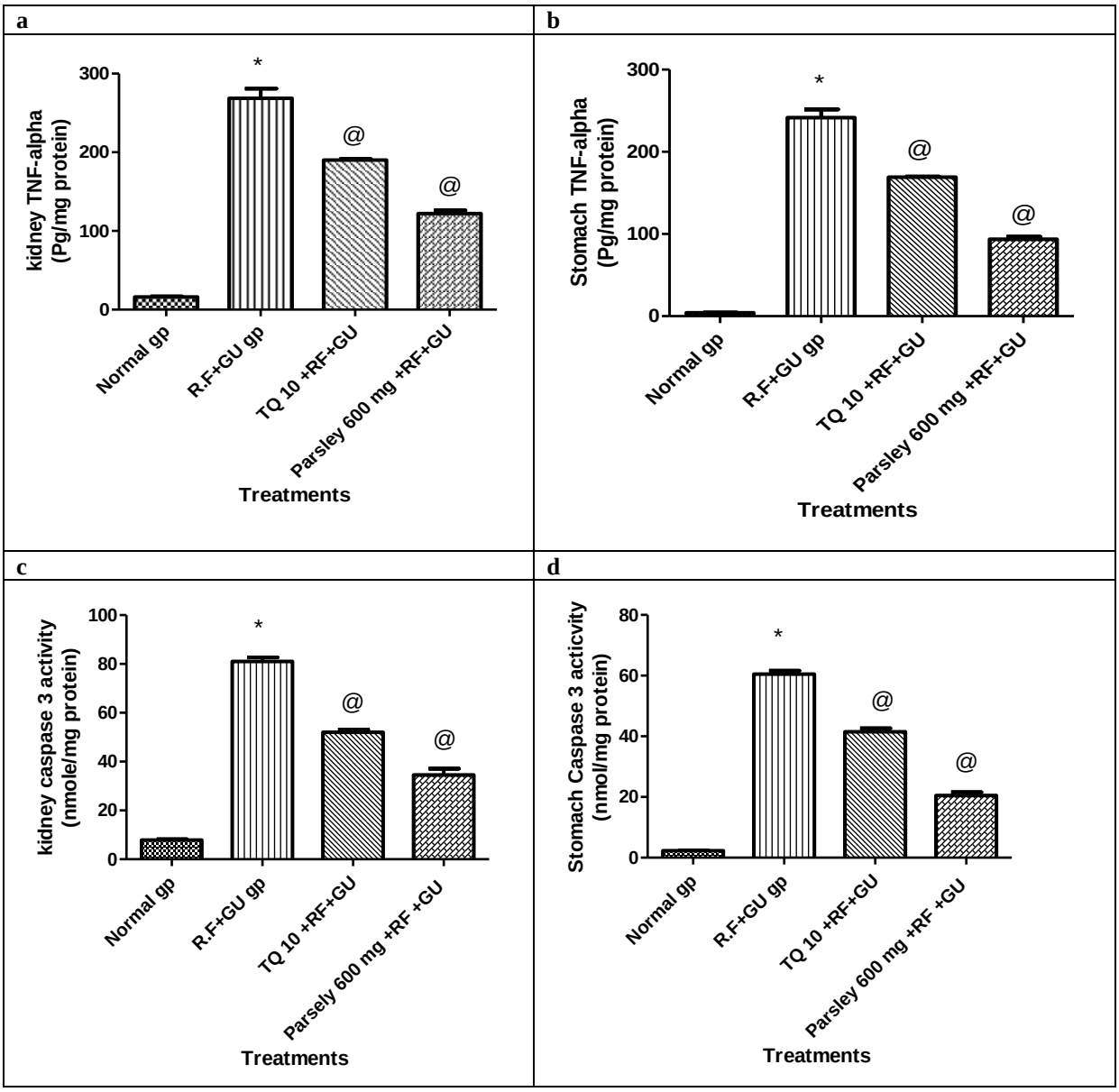

Fig 2 (a - d)
Effect of Thymoquinone and Parsley on tumor necrosis factor alpha and caspase 3 activity in glycerol - induced acute renal failure associated with gastric ulcer in rats.

(Group 1): Normal group (receiving Saline)
(Group 2): R.F + G.U group receiving Gly (8 ml/kg) +Ethanol (1ml/rat))
(Group 3): Group receiving thymoquinone (10 mg/kg), Gly (8 ml/kg) and Ethanol (1ml/rat)
(Group 4): Group receiving parsley (600 mg/kg), Gly (8 ml/kg) and Ethanol (1ml/rat)

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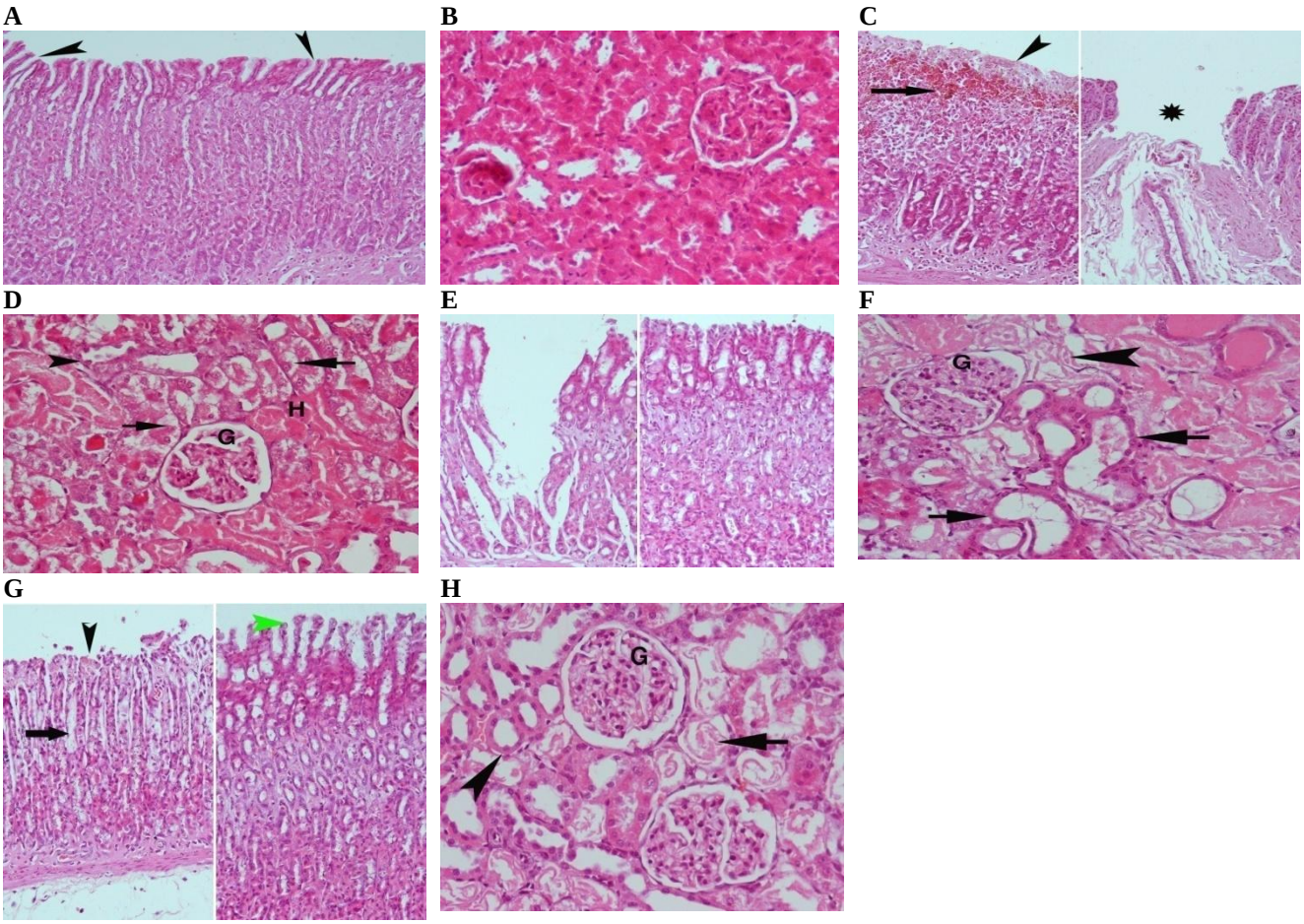

Fig.3 (A-H); Histopathological examination

(A) Represents normal stomach tissue
(B) Represents normal kidney tissue
(C)Stomach tissue of Rats subjected to renal failure and gastric ulcer.
(D) Renal tissue of Rats subjected to renal failure and gastric ulcer
(E) Stomach tissue of rats treated with thymoquinone
(F) Renal tissue of rats treated with thymoquinone
(G) Stomach tissue of rats treated with parsley
(H) Renal tissue of rats treated with parsley

Table 1: **Effect of Thymoquinone and Parsley on serum creatinine, creatinine clearance , blood urea nitrogen, urine volume and kidney weight / body weight ration in glycerol - induced acute renal failure associated with gastric ulcer in rats.**

Parameters Drugs &	SCr (mg/dl)	Cr cl (ml/min)	BUN (mg/dl)	Urine volume ml / 24 hr	Kw/Bw

Doses					
(Group 1)	0.57 ± 0.02	1.02 ± 0.03	24.43 ± 0.64	3.62± 0.28	0.0069 ± 0.0005
(Group 2)	2.54* ± 0.06	0.40* ± 0.01	71.80* ± 2.05	20.28* ± 1.47	0.0153* ± 0.0004
(Group 3)	1.89@ ± 0.02	0.57@ ±0.01	47.60 @ ± 1.435	13.40@ ± 0.24	0.0081 @ ± 0.0006
(Group 4)	1.71@ ± 0.029	0.68@ ± 0.01	43.50 @ ±1.17	9.16@ ± 0.83	0.008@ ±0.0004

(Group 1): Normal group (receiving Saline)
(Group 2): R.F + G.U group receiving Gly (8 ml/kg) +Ethanol (1ml/rat))
(Group 3): Group receiving thymoquinone (10 mg/kg), Gly (8 ml/kg) and Ethanol (1ml/rat)
(Group 4): Group receiving parsley (600 mg/kg), Gly (8 ml/kg) and Ethanol (1ml/rat)
Values are means of samples ± SEM. (n=9)
* Significant change compared with the normal group at $p<0.05$
@Significant change compared with R.F and G.U. group at $p<0.05$.

Table 2: Effect of Thymoquinone and Parsely on serum potassium and urine total protein in glycerol - induced acute renal failure associated with gastric ulcer in rats.

Parameters / Drugs & Doses	Serum K^+ mmol/l	UTP mg/24h
(Group 1)	3.78± 0.05	14.29 ± 0.68
(Group 2)	6.02* ± 0.14	84.00* ± 3.22
(Group 3)	4.82 @ ± 0.03	59.80@ ±2.08
(Group 4)	4.48@ ± 0.04	49.33@ ±0.84

(Group 1): Normal group (receiving Saline)
(Group 2): R.F + G.U group receiving (Gly (8 ml/kg) +Ethanol (1ml/rat))
(Group 3): Group receiving thymoquinone (10 mg/kg), Gly (8 ml/kg) and Ethanol (1ml/rat)
(Group 4): Group receiving parsley (600 mg/kg) , Gly (8 ml/kg) and Ethanol (1ml/rat)
Values are means of samples ± SEM. (n=9)
* Significant change compared with the normal group at $p<0.05$
@Significant change compared with R.F and G.U. group at $p<0.05$.

Table 3
Effect of Thymoquinone and Parsley on ulcer number and ulcer index in glycerol - induced acute renal failure associated with gastric ulcer in rats.

Parameters / Drugs & Doses	Ulcer number	Ulcer index
(Group 1)	0.00 ± 0.00	0.00 ± 0.00
(Group 2)	45.57* ± 2.09	97.29* ± 4.77
(Group 3)	16.00@ ± 1.36	30.63@ ± 1.99
(Group 4)	17.60@ ± 0.81	35.38@ ± 2.50

Group 1): Normal group (receiving Saline)
(Group 2): R.F + G.U group receiving (Gly (8 ml/kg) +Ethanol (1ml/rat))
(Group 3): Group receiving thymoquinone (10 mg/kg), Gly (8 ml/kg) and Ethanol (1ml/rat)
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Values are means of samples ± SEM. (n=9)
* Significant change compared with the normal group at $p<0.05$
@Significant change compared with R.F and G.U. group at $p<0.05$.

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