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Gum Acacia mitigates diclofenac nephrotoxicity by targeting monocyte chemoattractant protein-1, complement receptor-1 and pro-apoptotic pathways

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A B S T R A C T

Treatment of many inflammatory diseases involves a chronic use of NSAIDs in large doses increasing acute kidney injury risk. This study was designed to evaluate a potential renoprotective effect of Gum Acacia (GA) on diclofenac (DICF) induced nephrotoxicity. Six groups of rats were used: normal group; control group (deprived from water during week 13), DICF group (deprived from water during week 13 and injected DICF i.p. 15 mg/kg/12 h at days 4 through 6 of water deprivation days, GA groups (1, 2 or 3 g/kg/day in drinking water) for 12 weeks followed by water deprivation and DICF injection as described. Kidney function, oxidative stress and antioxidant biomarkers were measured. Interleukin-1β, IL-10, TNF-α, complement receptor (CR)-1, monocyte chemoattractant protein (MCP)-1 and caspase-3 were assessed. Kidney sections were scored for fibrosis, tubular injury and inflammatory cells. An elevation in renal biomarkers, inflammatory cytokines, malondialdehyde and apoptotic markers was observed after DICF injection ($p < 0.001$). Gum Acacia (mostly 3 g/kg) markedly reduced fibrosis, tubular injury, IL-1β, TNF-α, caspase-3 and MCP-1 levels ($p < 0.01$). It increased IL-10, antioxidant capacity, CR-1 level in the kidney ($p < 0.001$). Protective effect may be mediated by antioxidant, anti-inflammatory and anti-apoptotic mechanisms besides interfering with monocytes and complement mediated tissue damage pathways.

1. Introduction

Nephrotoxicity is a challenging side effect of many non-steroidal anti-inflammatory drugs (NSAIDs). Diclofenac (DICF) is one of the widely used NSAID that has been associated with many kinds of renal tissue damage especially when misused in large doses (Aydin et al., 2003). It is well established that DICF is a powerful nephrotoxicant and it causes massive genomic DNA fragmentation and necrotic cell death leading to destruction of proximal and distal convoluted tubules and subsequently acute renal injury (Hickey et al., 2001; Ng et al., 2008).

Acute renal injury may be hemodynamically mediated through decreasing prostaglandins and in turn reducing renal flow and/or disrupting the compensatory vasodilation responses (Ulinski et al., 2004). In addition, injury may be immune mediated through interstitial infiltration of inflammatory cells; the major cause of drug induced acute kidney injury (Perazella and Markowitz, 2010).

Gum Acacia (GA) is used in the traditional medicinal practices especially in Middle Eastern countries. Some reports have claimed that GA possesses antioxidant, nephroprotectant and other beneficial anti-inflammatory effects on gastrointestinal tract (Ali et al., 2009). Many studies have evaluated the effect of GA on experimental models of kidney diseases and reported its ability to limit their progression (Ali et al., 2013; Matsumoto et al., 2006). Treatment with GA was found to increase creatinine clearance, decreases plasma phosphate concentration, proteinuria and urinary excretion of phosphate and sodium. These effects may account for GA benefits in chronic renal failure and diabetic nephropathy (Nasir, 2013).

This study was designed to investigate possible protective effect of GA against nephrotoxic effects of DICF in an experimental model of acute kidney injury.

Abbreviations: CR, complement receptor; DICF, Diclofenac; GA, Gum Acacia; H&E, hematoxylin-eosin; IL, interleukin; i.p, intraperitoneal; GSH, reduced glutathione; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; NSAID, non-steroidal anti-inflammatory drug; TNF, tumor necrosis factor

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2. Materials

Seventy adult male *Wistar* rats weighing 200 ± 20 g were purchased from VACSERA (Giza, Egypt). During acclimatization, rats were allowed free access to food and water. Animal care and experimental procedures were in accordance with the ethical guidelines adopted by the Guide for the Care and Use of Laboratory Animals (8th edition, National Academies Press). The study protocol was reviewed and approved by the Scientific Research Ethics Committee, Faculty of Pharmacy, Mansoura University (code number: 2018–104).

Gum Acacia (100% pure *Acacia Senegal* E − 414 powder of HASHAB grade) was purchased from UAE. Diclofenac potassium was purchased as ampoules (75 mg/3 ml) from Novartis Pharmaceuticals Corporation (PubChem CID: 23667642 UNII-L4D5UA6CB4).

2.1. Experimental protocol

After an acclimatization period of 14 days, rats were randomly divided into six groups as follows: *Normal group* (n = 8): rats were injected 0.6 ml/kg 0.9% w/v saline (i.p., twice a day, at days 4 through 6 in the week 13 of the experiment); *Control group* (n = 8): rats were deprived from water during week 13 of the experiment and were injected saline as described in normal group; *DICF group* (n = 15): rats were deprived from water during week 13 of the experiment and injected DICF 15 mg/kg (2.5% w/v, 0.6 ml/kg/12 h, i.p.) at days 4 through 6 of water deprivation days; *GA groups:* three groups (n = 15 each) received GA (1, 2 or 3 g/kg/day in drinking water in concentrations 1, 2 or 3% w/v respectively for 12 weeks) then rats were deprived of water and injected DICF as described in DICF group. The experimental design is illustrated by a schematic presentation in Table 1.

Tested model of acute kidney injury by water deprivation and DICF injection was carried out in accordance to Efrati et al., 2007. Doses of GA were selected in the light of a sub-chronic toxicity study carried out by Doi et al., 2006.

3. Methods

3.1. Kidney function biomarkers

After the last DICF injection by 24 h, rats were anaesthetized by an i.p. injection of thiopental (50 mg/kg) and blood samples were collected through cardiac puncture, centrifuged at 4 °C for 10 min (3000 rpm), serum was separated, divided into aliquots (to avoid freeze–thaw cycles) and stored at − 20 °C. Serum creatinine, urea and uric acid (Biomed Diagnostics, Egy-Chem, Egypt) were measured in mg/dl spectrophotometrically according to the manufacturer's instructions.

Table 1
Schematic representation of experimental protocol.

Group	Week 1 → 12	Week 13		
		Day 1 → 3	Day 4 → 6	Day 7
Normal	○	← Water	□	Sacrifice
Control	○	Deprivation →	← Water	□
DICF	○		Deprivation→	■
GA (1 g/kg)	☼			■
GA (2 g/kg)	☼☼			■
GA (3 g/kg)	☼☼☼			■

DICF: diclofenac, GA: Gum Acacia.
Rats received food moistened with water (water/food: 10% w/w).
○: rats received 100 ml/kg/day drinking water.
☼, ☼☼, ☼☼☼: rats received 1, 2 or 3% w/v GA respectively in drinking water (100 ml/kg/day).
□: rats were injected saline (0.9% w/v; i.p; 0.6 ml/kg/12 h).
■: rats were injected 15 mg/kg/day DICF (2.5% w/v, 0.6 ml/kg/12 h).

3.2. Oxidative stress and antioxidant biomarkers

Isolated kidneys were cut into pieces and homogenized in ice cooled phosphate buffer saline (10% w/v, pH 7.4) using a manual glass homogenizer then centrifuged at 5000 rpm for 20 min at 4 °C and the supernatant was separated. Lipid peroxidation was estimated by quantification of malondialdehyde (MDA) level (nmol/g tissue) using the method of Ohkawa et al., 1979 that is based on the reaction of thiobarbituric acid with MDA then measuring the absorbance at 534 nm.

Catalase activity was determined in tissue homogenate according to the method of Aebi, 1985 and absorbance was measured at 510 nm.

Reduced glutathione (GSH) and total antioxidant capacity were measured using commercially available kits (Bio-diagnostic, Giza Egypt) spectrophotometrically at 405 and 505 nm respectively.

3.3. Histopathological examination

Kidneys were cut longitudinally, fixed in 10% neutral buffered formalin and sent for pathological evaluation. Paraffin wax blocks were prepared and sections of 4 μm in thickness were examined for tubular injury and interstitial fibrosis.

Tubular injury was scored in hematoxylin-eosin (H&E) stained sections under light microscope using the scoring system modified by Kinomura et al., 2008. Briefly, twenty randomly selected fields were examined (X400) and tubular injury (desquamation from the tubular basement membrane, swelling, vacuolar degeneration and necrosis) was quantified with a score (0–5) where: 0: normal; 1: < 20% of the tubules are involved; 2: 20–40%; 3: 40–60%; 4: 60–80%; and 5: 80–100%.

Interstitial fibrosis was quantified in Masson trichrome stained sections using a color image analyzer (Image J 1.32). In five randomly selected fields, the fibrotic area was measured in the OSOM and corticomedullary junction avoiding the blood vessels as described by Yamate et al., 1995.

For inflammatory cells count, ten fields with maximum aggregates of inflammatory cells (polymorph-nuclear leukocytes with segmented nuclei and macrophages) were counted for each group and the average number was taken for each group.

3.4. ELISA measurements

Levels of interleukin (IL)-1β, IL-10, TNF (tumor necrosis factor)-α, monocyte chemoattractant protein (MCP)-1 (*eBioscience*; Vienna, Austria), caspase-3, procollagen type III amino terminal peptide (PIIINP) (*USCNK*; Wuhan, China) and complement receptor (CR)-1 (*ASSAY Kit CO. Ltd*, USA) were measured according to the manufacturers' instructions.

3.5. Statistical analysis

Data are expressed as mean ± S.E. Results were statistically tested using one way analysis of variance (ANOVA), followed by the post-Hoc test (Tukey–Kramer multiple comparison test). Histopathological scores were compared by Kruskal Wallis test by rank followed by Dunn's multiple comparison test. GraphPad Prism V5.01 (GraphPad Software Inc, San Diego, CA, USA) was used to perform statistical tests and construct figures.

4. Results

Water deprivation alone for 6 days did not significantly change kidney function biomarkers from its normal levels in control group. In DICF group, injection of DICF (15 mg/kg) during the last 3 days of water deprivation was associated with significant changes in kidney function as it elevated serum creatinine, urea and uric acid levels

Table 2
Effects of Gum Acacia (1, 2, 3 g/kg) administration on serum levels of kidney function biomarkers (creatinine, urea and uric acid) in diclofenac induced nephropathy in rats.

Group	Creatinine	Urea	Uric acid
	(mg/dl)	(mg/dl)	(mg/dl)
Normal	5.78 ± 0.49	61.89 ± 4.20	3.09 ± 0.22
Control (water deprivation)	6.08 ± 0.37	62.08 ± 2.11	3.95 ± 0.15
DICF (15 mg/kg)	22.0 ± 0.66***	101.2 ± 1.99***	5.27 ± 0.49***
DICF + GA			
(1 g/kg)	9.57 ± 0.15***†	96.76 ± 2.60***	4.57 ± 0.45*
(2 g/kg)	7.22 ± 0.10†‡	73.35 ± 3.04†,‡	4.22 ± 0.26
(3 g/kg)	6.68 ± 0.24†‡	52.62 ± 4.21†‡§	2.99 ± 0.16†‡§

DICF: diclofenac, GA: Gum Acacia.
*, ***P < 0.05, 0.001 respectively compared to normal and control groups.
†P < 0.001 compared to DICF group.
‡P < 0.05 compared to DICF + GA (1 g/kg).
§P < 0.05 compared to DICF + GA (2 g/kg).

significantly (p < 0.001) compared to both normal and control groups [Table 2]. Administration of GA (1, 2 or 3 g/kg/day) in drinking water for 12 weeks before induction of kidney injury decreased serum creatinine (p < 0.001) compared to DICF group. The decrease in serum creatinine in groups received 2 and 3 g/kg GA was more significant compared to 1 g/kg GA (p < 0.05). Urea levels were significantly (p < 0.001, 0.05) less in groups received 2 and 3 g/kg GA compared to its level in groups received DICF alone or when preceded by 1 g/kg GA respectively. Meanwhile, uric acid level was decreased to normal only in DICF + 3 g/kg GA group compared to DICF alone, DICF + 1 g/kg GA and DICF + 2 g/kg GA groups (p < 0.001, 0.05 and 0.05 respectively).

Injection of DICF associated with water deprivation resulted in generation of reactive oxygen species (ROS) and marked lipid peroxidation indicated by elevation of MDA level in renal tissue significantly (p < 0.001) compared to both normal and control groups [Fig. 1A]. Gum Acacia (1, 2 and 3 g/kg) decreased MDA level significantly and the lowest level was observed in DICF + 3 g/kg GA group when compared to other GA groups (p < 0.001).

Total antioxidant capacity in renal tissue was significantly (p < 0.01, 0.001) elevated in groups received 2 or 3 g/kg GA compared to DICF alone or DICF + 1 g/kg GA [Fig. 1B]. Similarly, GSH level and catalase activity were significantly (p < 0.001) high in groups received 2 or 3 g/kg GA and they were comparable to normal values in the latter group [Fig. 1C and D].

Histopathological examination revealed prominent tubular interstitial injury in the DICF/water deprivation group in the form of tubular damage, epithelial desquamation and infiltration of mixed chronic inflammatory cells [Fig. 2A, upper panel]. Tubular injury score and inflammatory cells count were significantly decreased by GA (p < 0.001) compared to DICF group. Infiltration of inflammatory cells and injury score in DICF + GA (3 g/kg) was significantly (p < 0.01) lower than DICF + GA (1 g/kg) [Table 3]. A marked decrease in interstitial fibrosis was observed in DICF + GA received groups mostly in DICF + GA (3 g/kg) group [Fig. 2A, lower panel]. Serum level of the fibrosis marker PIIINP was significantly increased (p < 0.001) after DICF injection compared with normal and control groups [Fig. 2B]. Only GA (3 g/kg) decreased serum PIIINP level significantly (p < 0.001) compared with its level in groups received DICF, DICF + GA (1 g/kg) or DICF + GA (2 g/kg).

Renal levels of MCP-1 [Fig. 3] were significantly (p < 0.001) decreased by administration of 1, 2 or 3 g/kg GA compared to its level in DICF group but they still significantly higher than control group level (p < 0.05). The renal expression of the death ligand TNF-α was increased in DICF group compared to control group (p < 0.001) and the level of caspase-3 was elevated in turn. Caspase-3 and TNF-α levels were significantly lowered most notably in DICF + 3 g/kg GA group (p < 0.001) compared to DICF, DICF + 1 g/kg GA and DICF + 2 g/kg GA groups [Fig. 4A and B].

Level of IL-1β was significantly high in DICF group compared to normal and control groups (p < 0.001). This level was lowered in all groups that received GA prior to DICF (p < 0.001) when compared to the group that received DICF alone [Fig. 5].

Injection of DICF with water deprivation significantly decreased renal CR-1 expression [Fig. 6A] compared to control group. Receiving GA (2 and 3 g/kg) significantly increased CR-1 level in kidney tissue (p < 0.001) but it remained significantly lower than normal (p < 0.05).

Level of the anti-inflammatory marker IL-10 [Fig. 6B] was not significantly changed from normal level after DICF injection. Group received DICF + GA (3 g/kg) showed a significant elevation in IL-10 level compared to all tested groups (p < 0.01).

5. Discussion

The present study was designed to investigate a potential renoprotective effect of GA against DICF induced renal toxicity. The experimental protocol included administration of DICF along with water deprivation; a reliable and convenient model of renal insufficiency characterized by severe vasoconstriction, low renal blood flow, extensive tubular necrosis and deterioration of vital renal functions (Efrati et al., 2007).

Diclofenac with water deprivation resulted in significant histopathological changes in renal tissue including interstitial inflammation, tubular injury and fibrosis. Moreover, DICF elevated MDA level indicating lipid peroxidation and ROS production. Although the exact mechanism underlying DICF nephrotoxicity is still poorly understood, oxidative stress initiated during its metabolism may underlie the resultant renal injury (Hickey et al., 2001). Scavenging ROS has been considered as a popular approach against renal cells injury and apoptosis induced by nephrotoxic drugs.

Administration of GA (3 g/kg/day) for 4 weeks before DICF reserved normal levels of renal function biomarkers (serum creatinine, urea and uric acid levels). It also activated endogenous antioxidant enzymes (catalase, GSH) and elevated total antioxidant content. A similar renoprotective effect of GA that involved an anti-oxidant action was obtained in an adenine induced kidney failure model carried out by Ali et al. (2010).

An increase in MCP-1 level was observed in the group received DICF alone. Kidney cells produce MCP-1 in response to a variety of pro-inflammatory stimuli, and predictably, its expression has been identified in kidney diseases which involve significant inflammation (Tesch, 2008). It is a major promoter of inflammation and renal injury response that may lead to renal fibrosis (Giunti et al., 2010). In addition, it plays a major role in the pathogenesis and progression of renal failure and its expression correlates with the degree of renal damage in models of glomerular injury (Panzer et al., 2001).

Many studies provide evidence that increased concentrations of MCP-1 in the diseased kidney increases production of cytokines and adhesion molecules leading to glomerulonephritis and tubulointerstitial inflammation. It increases the proinflammatory cytokine interleukin-6, the intracellular adhesion molecule-1 and activates nuclear factor-κB and activating protein-1 (Viedt et al., 2002).

Different doses of GA tested in our study decreased renal expression of MCP-1 when administered before DICF injection supposing a mechanism for its renal protective effect. In line with our results, decreasing MCP-1 RNA-expression by GA may account for decreasing risk of metabolic syndrome and visceral abdominal fat deposition (Ushida et al., 2011). Since, decreasing expression of MCP-1 and/or blockade of its receptors can reduce interstitial inflammation and fibrosis (Vielhauer et al., 2004), its reduced level may account for the decrease in the inflammatory cytokines TNF-α and IL-1β in groups that received

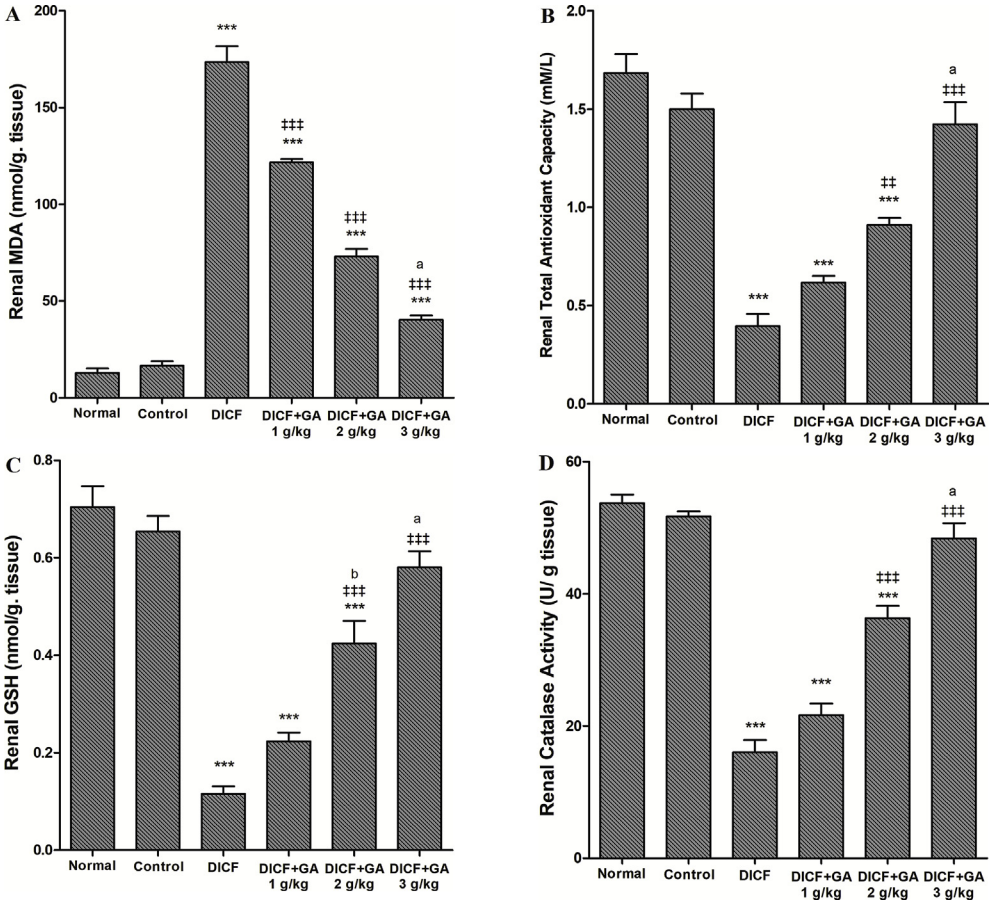

Fig. 1. Effects of 1, 2 or 3 g/kg Gum Acacia (GA) on renal tissue levels of A) malondialdehyde (MDA) B) total antioxidant capacity C) reduced glutathione (GSH) and D) catalase in water deprivation/diclofenac (DICF, 15 mg/kg) induced nephropathy in rats (n = 6); ***p < 0.001 compared with control group; ‡‡, ‡‡‡p < 0.01, 0.001 compared with DICF group; [a] p < 0.05 compared with DICF + GA 1 or 2 g/kg groups, [b]p < 0.05 compared with DICF + GA 1 g/kg group.

GA.

Apoptosis regulators have been used recently as therapeutic strategies that modulate cellular life-and-death decisions. The death ligand TNF-α can trigger extrinsic proapoptotic signalling in stressed tubular epithelial cells and can be found in the kidney following nephrotoxic insults (Ortiz et al., 2000). The protective effect of GA against nephrotoxicity may be attributed to the reduction of TNF-α production and ensuing dampening of death receptor signalling then apoptosis as indicated by lower caspase-3 level in groups received GA before DICF.

Our study suggests that DICF nephrotoxicity may be partly mediated

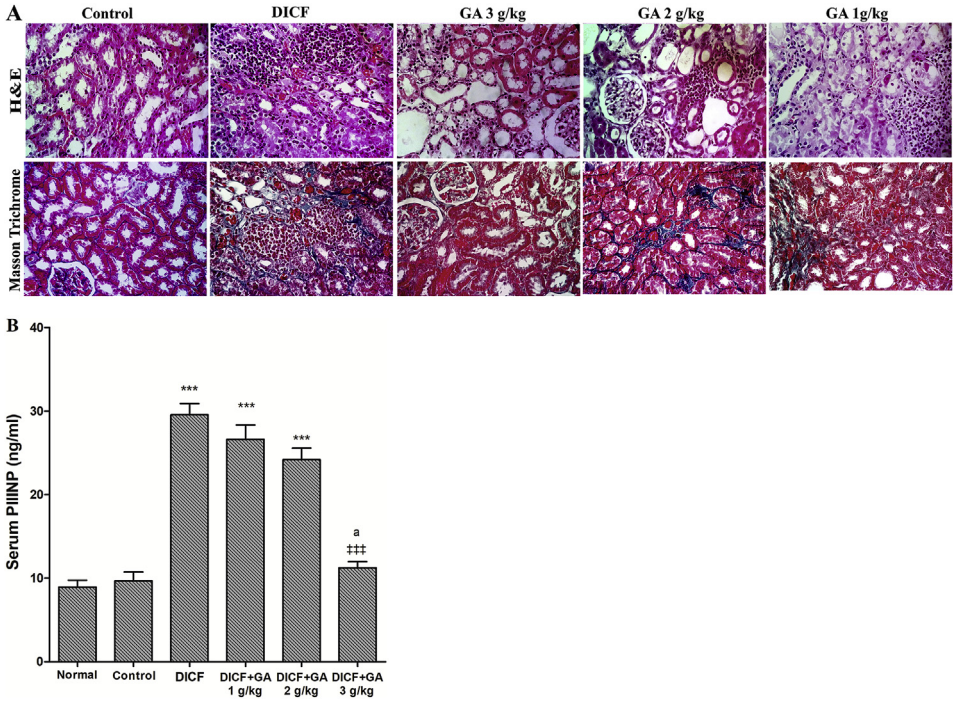

Fig. 2. A) Representative images of histopathology examined kidney sections stained with i. Hematoxylin-eosin (upper panel) showing marked improvement in interstitial injury and lower infiltration of inflammatory cells by Gum Acacia (GA, 3 g/kg) compared to GA (1 or 2 g/kg) and diclofenac (DICF). ii. Masson trichrome (lower panel) showing marked reduction in collagen deposition and fibrosis in GA (3 g/kg) group compared to DICF (X400). B) Effects of 1, 2 or 3 g/kg Gum Acacia (GA) on serum level of procollagen type III amino terminal peptide (PIIINP) in water deprivation/diclofenac (DICF, 15 mg/kg) induced nephropathy in rats (n = 6); ***p < 0.001 compared with control group; ‡‡‡p < 0.001 compared with DICF group, [a] p < 0.001 compared with DICF + GA 1 or 2 g/kg groups.

Table 3
Effects of Gum Acacia (1, 2, 3 g/kg) administration on fibrosis and renal tubular injury scores in diclofenac induced model of nephropathy in rats.

Group	Fibrosis score	Tubular injury score	Inflammatory cells count (10 fields)
Normal	1.087 ± 0.026	0.000 ± 0.000	0.000 ± 0.000
Control	1.092 ± 0.032	0.000 ± 0.000	0.000 ± 0.000
DICF (15 mg/kg)	3.821 ± 0.254***	3.950 ± 0.185	118.7 ± 2.955
DICF + GA			
(1 g/kg)	2.881 ± 0.169***	2.650 ± 0.167††	88.20 ± 1.073
(2 g/kg)	2.286 ± 0.126*	2.100 ± 0.161†††	69.40 ± 1.087†††
(3 g/kg)	1.689 ± 0.112††‡	1.550 ± 0.135††‡	59.00 ± 0.596††‡

DICF: diclofenac, GA: Gum Acacia.
*, ***P < 0.05, 0.001 respectively compared to normal and control groups.
††, †††P < 0.01, 0.001 respectively compared to DICF group.
‡P < 0.01 compared to DICF + GA (1 g/kg).

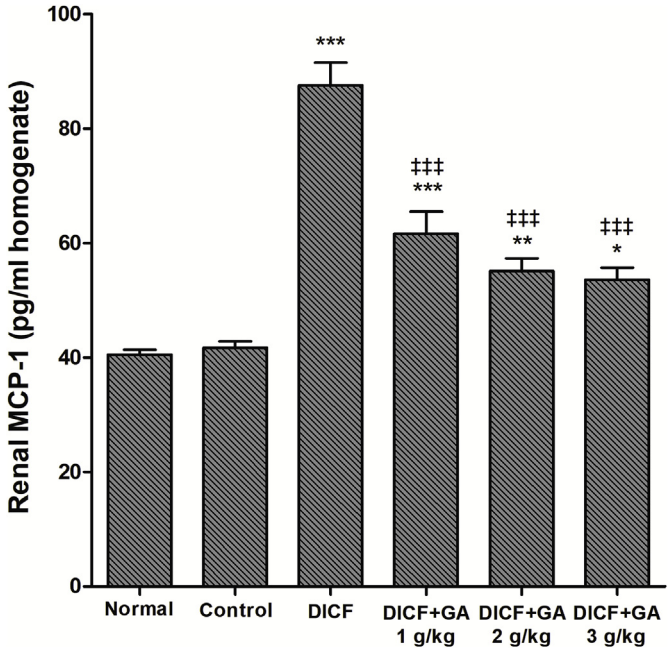

Fig. 3. Effects of 1, 2 or 3 g/kg Gum Acacia (GA) on renal tissue levels of monocyte chemoattractant protein (MCP)-1 in water deprivation/diclofenac (DICF, 15 mg/kg) induced nephropathy in rats (n = 6); *, **, ***p < 0.05, 0.01, 0.001 respectively compared with control group; ‡‡‡p < 0.001 compared with DICF group.

by complement activation as indicated by reduced level of renal CR-1. Many types of renal tissue damage have been related to activation of complement system such as ketoprofen induced acute kidney injury (Palviainen et al., 2015) and adriamycin induced nephropathy (Turnberg et al., 2006).

Vieyra and Heeger (2010) showed that activation of the complement system in the kidney tissue is firmly related to dysregulation of complement receptors. Lately, CR-1 has emerged as a therapeutic target for complement dependent inflammatory reactions during different nephropathies. It is the only physiological inhibitor of complement on podocytes and it is lost in different glomerulopathies by proteolytic removal from the cell membrane (Moll et al., 2001). Reduced expression of CR-1 on the glomerulus in patients with diffuse proliferative glomerulonephritis has been reported compared with expression in normal subjects (Arora et al., 2000). It was suggested that CR-1 controls the amplification of complement at the critical step of C3 activation. It decreases C3b deposition and accelerates its cleavage during both classical and alternative pathways (Java et al., 2015).

Injection of DICF and water deprivation were associated with a

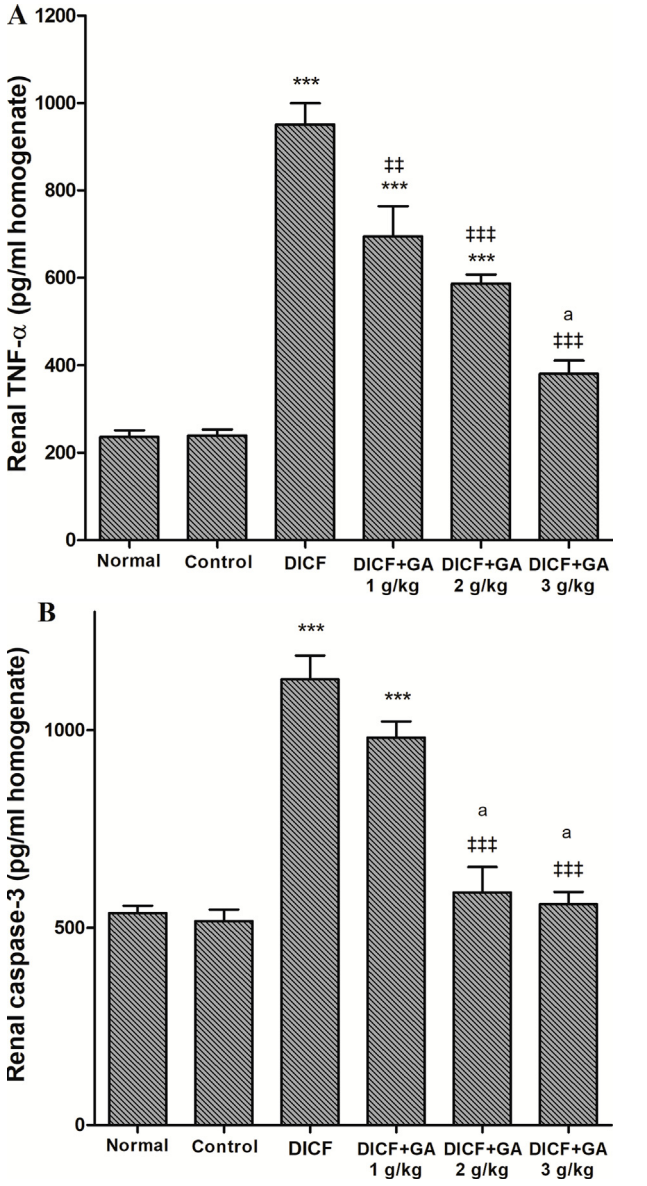

Fig. 4. Effects of 1, 2 or 3 g/kg Gum Acacia (GA) on renal tissue levels of A) tumor necrosis factor (TNF)-α B) caspase-3 in water deprivation/diclofenac (DICF, 15 mg/kg) induced nephropathy in rats (n = 6); ***p < 0.001 compared with control group; ‡‡, ‡‡‡p > 0.01, 0.001 compared with DICF group; ^{a} p < 0.05 compared with DICF + GA 1 g/kg group.

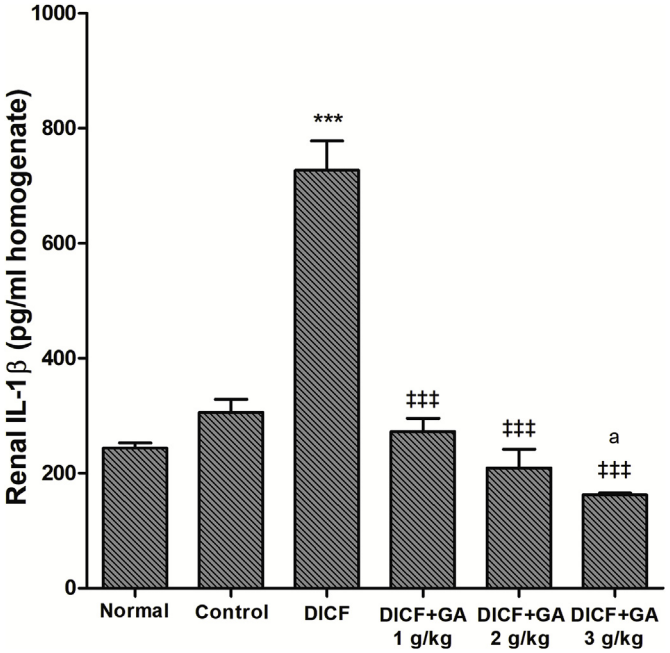

Fig. 5. Effects of 1, 2 or 3 g/kg Gum Acacia (GA) on renal tissue levels of interleukin (IL)-1β in water deprivation/diclofenac (DICF, 15 mg/kg) induced nephropathy in rats (n = 6); ***p < 0.001 compared with control group; ‡‡‡p < 0.001 compared with DICF group; [a] p < 0.05 compared with DICF + GA 1 g/kg group.

decrease in renal tissue level of CR-1 in the group received DICF and deprived from water. This reduced level allows complement-mediated inflammatory reactions and subsequent organ damage. Gum Acacia elevated CR1 expression in renal tissue that has been considered the chain breaker of complement pathways (Khera et al., 2009).

The anti-inflammatory cytokine IL-10 can halt inflammatory and cytotoxic pathways involved in various renal injuries (Deng et al., 2001; Tadagavadi and Reeves, 2010). Effect of DICF on IL-10 expression is controversial and may be influenced by the dose tested. Decreased levels of IL-10 were observed in patients with DICF hepatotoxicity (Aithal et al., 2004). On the other hand, administration of DICF in patients undergoing major surgery elevated IL-10 modulating inflammatory response (Mahdy et al., 2002). Our results showed a slight decrease in IL-10 kidney level by DICF (not significant from control group). Pretreatment with large dose of GA increased IL-10 level adding an additional protective mechanism against DICF induced renal injury. The increased IL-10 level may be due to ability of GA to modify dendritic cells function including maturation, phagocytic activity and cytokines release (Xuan et al., 2010; Nasir, 2013).

6. Conclusion

The obtained results suggest a protective effect of GA against DICF induced nephrotoxicity possibly through antioxidant anti-inflammatory mechanisms. It also interferes with monocytes and complement mediated inflammatory pathways. Finally, it may have an anti-apoptotic effect limiting renal tissue damage and dysfunction. However, further studies are recommended to investigate the effect of GA as a post-treatment in kidney injury and since it is a natural dietary supplement clinical studies are warranted to ensure its renoprotective benefits.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.04.050.

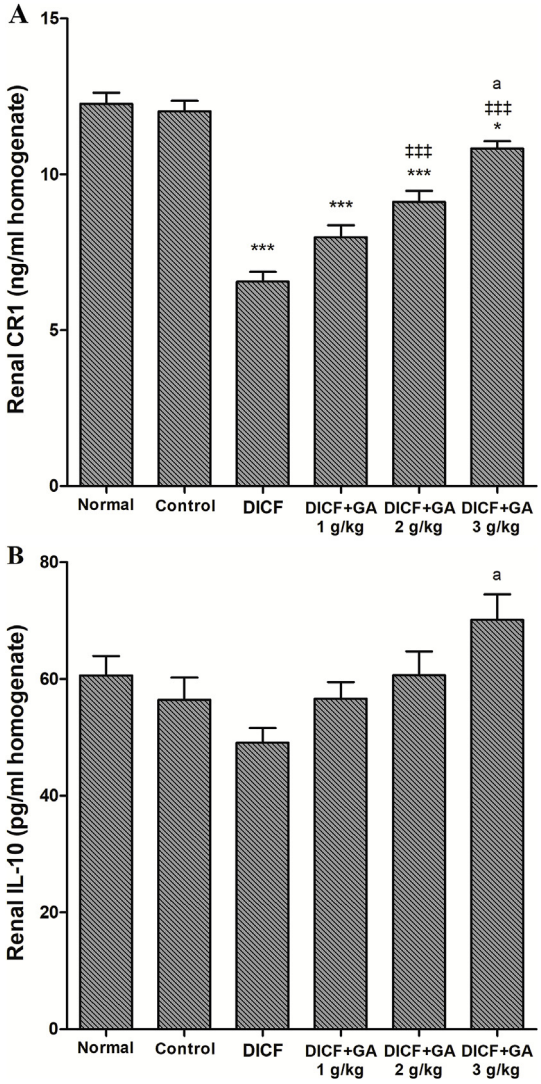

Fig. 6. Effects of 1, 2 or 3 g/kg Gum Acacia (GA) on renal tissue levels of A) complement receptor (CR)-1 B) interleukin (IL)-10 in water deprivation/diclofenac (DICF, 15 mg/kg) induced nephropathy in rats (n = 6); *, ***p < 0.05, 0.001 compared with control group; ‡‡‡p < 0.001 compared with DICF group; [a] p < 0.01 compared with DICF + GA 1 or 2 g/kg groups.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

Aebi, H.E., 1985. Catalase. In: Bergmeyer, H.U., Bergmeyer, J., Grabi, M. (Eds.), Methods of Enzymatic Analysis. Verlag Chimie, Weinheim, pp. 273–286.

Aithal, G.P., Ramsay, L., Daly, A.K., Sonchit, N., Leathart, J.B., Alexander, G., Kenna, J.G., Caldwell, J., Day, C.P., 2004. Hepatic adducts, circulating antibodies, and cytokine polymorphisms in patients with diclofenac hepatotoxicity. Hepatology 39, 1430–1440.

Ali, B.H., Al-Husseni, I., Beegam, S., Al-Shukaili, A., Nemmar, A., Schierling, S., Queisser, N., Schupp, N., 2013. Effect of gum Arabic on oxidative stress and inflammation in adenine–induced chronic renal failure in rats. PLoS One 8, e55242.

Ali, B.H., Al-Salam, S., Al Husseni, I., Kayed, R.R., Al-Masroori, N., Al-Harthi, T., Al Zaabi, M., Nemmar, A., 2010. Effects of Gum Arabic in rats with adenine-induced chronic renal failure. Exp. Biol. Med. 235, 373–382.

Ali, B.H., Ziada, A., Blunden, G., 2009. Biological effects of gum Arabic: a review of some recent research. Food Chem. Toxicol. 47, 1–8.
Arora, M., Arora, R., Tiwari, S.C., Das, N., Srivastava, L.M., 2000. Expression of complement regulatory proteins in diffuse proliferative glomerulonephritis. Lupus 9, 127–131.
Aydin, G., Gökçimen, A., Öncü, M., Çicek, E., Karahan, N., Gökalp, O., 2003. Histopathologic changes in liver and renal tissues induced by different doses of diclofenac sodium in rats. Turk. J. Vet. Anim. Sci. 27, 1131–1140.
Deng, J., Kohda, Y., Chiao, H., Star, R.A., 2001. MSH acts in part via IL-10 to inhibit ischemic and nephroxic ARF. J. Am. Soc. Nephrol. 12, 800A.
Doi, Y., Ichihara, T., Hagiwara, A., Imai, N., Tamano, S., Orikoshi, H., Ogasawara, K., Sasaki, Y., Nakamura, M., Shirai, T., 2006. A ninety-day oral toxicity study of new type of processed gum Arabic, from Acacia tree (Acacia Senegal) exudates, in F344 rats. Food Chem. Toxicol. 44, 560–566.
Efrati, S., Berman, S., Siman-Tov, Y., Lotan, R., Averbukh, Z., Weissgarten, J., Golik, A., 2007. N-acetylcysteine attenuates NSAID-induced rat renal failure by restoring intrarenal prostaglandin synthesis. Nephrol. Dial. Transplant. 22, 1873–1881.
Giunti, S., Barutta, F., Cavallo Perin, P., Gruden, G., 2010. Targeting the MCP-1/CCR2 system in diabetic kidney disease. Curr. Vasc. Pharmacol. 8 849-460.
Hickey, E.J., Raje, R.R., Reid, V.E., Gross, S.M., Ray, S.D., 2001. Diclofenac induced in vivo nephrotoxicity may involve oxidative stress-mediated massive genomic DNA fragmentation and apoptotic cell death. Free Radic. Biol. Med. 31, 139–152.
Java, A., Liszewski, M.K., Hourcade, D.E., Zhang, F., Atkinson, J.P., 2015. Role of complement receptor 1 (CR1; CD35) on epithelial cells: a model for understanding complement-mediated damage in the kidney. Mol. Immunol. 67, 584–595.
Khera, R., Das, N., 2009. Complement Receptor 1: disease associations and therapeutic implications. Mol. Immunol. 46, 761–772.
Kinomura, M., Kitamura, S., Tanabe, K., Ichinose, K., Hirokoshi, K., Takazawa, Y., Kitayama, H., Nasu, T., Sugiyama, H., Yamasaki, Y., Sugaya, T., 2008. Amelioration of cisplatin–induced acute renal injury by renal progenitor–like cells derived from the adult rat kidney. Cell Transplant. 17, 143–158.
Mahdy, A.M., Galley, H.F., Abdel-Wahed, M.A., El-Korny, K.F., Sheta, S.A., Webster, N.R., 2002. Differential modulation of interleukin-6 and interleukin-10 by diclofenac in patients undergoing major surgery. Br. J. Anaesth. 88, 797–802.
Matsumoto, N., Riley, S., Fraser, D., Al-Assaf, S., Ishimura, E., Wolever, T., Phillips, G.O., Phillips, A.O., 2006. Butyrate modulates TGF-β1 generation and function: potential renal benefit for Acacia (sen) SUPERGUM™(gum Arabic)? Kidney Int. 69, 257–265.
Moll, S., Miot, S., Sadallah, S., Gudat, F., Mihatsch, M.J., Schifferli, J.A., 2001. No complement receptor 1 stumps on podocytes in human glomerulopathies. Kidney Int. 59, 160–168.
Nasir, O., 2013. Renal and extrarenal effects of gum Arabic (Acacia Senegal)-What can be learned from animal experiments? Kidney and blood press. Res. 37, 269–279.
Ng, L.E., Halliwell, B., Wong, K.P., 2008. Nephrotoxic cell death by diclofenac and meloxicam. Biochem. Biophys. Res. Commun. 369, 873–877.
Ohkawa, H., Ohishi, N., Yagi, K., 1979. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal. Biochem. 95, 351–358.
Ortiz, A., Lorz, C., Catalan, M.P., Danoff, T.M., Yamasaki, Y., Egido, J., Neilson, E.G., 2000. Expression of apoptosis regulatory proteins in tubular epithelium stressed in culture or following acute renal failure. Kidney Int. 57, 969–981.
Palviainen, M.J., Junnikkala, S., Raekallio, M., Meri, S., Vainio, O., 2015. Activation of complement system in kidney after ketoprofen-induced kidney injury in sheep. Acta Vet. Scand. 57, 15.
Panzer, U., Thaiss, F., Zahner, G., Barth, P., Reszka, M., Reinking, R.R., Wolf, G., Helmchen, U., Stahl, R.A., 2001. Monocyte chemoattractant protein-1 and osteopontin differentially regulate monocytes recruitment in experimental glomerulonephritis. Kidney Int. 59, 1762–1769.
Perazella, M.A., Markowitz, G.S., 2010. Drug-induced acute interstitial nephritis. Nat. Rev. Nephrol. 6, 461.
Tadagavadi, R.K., Reeves, W.B., 2010. Endogenous IL-10 attenuates cisplatin nephrotoxicity: role of dendritic cells. J. Immunol. 185, 4904–4911.
Tesch, G.H., 2008. MCP-1/CCL2: a new diagnostic marker and therapeutic target for progressive renal injury in diabetic nephropathy. Am. J. Physiol. Renal. Physiol. 294, F697–F701.
Turnberg, D., Lewis, M., Moss, J., Xu, Y., Botto, M., Cook, H.T., 2006. Complement activation contributes to both glomerular and tubulointerstitial damage in adriamycin nephropathy in mice. J. Immunol. 177, 4094–4102.
Ulinski, T., Guigonis, V., Dunan, O., Bensman, A., 2004. Acute renal failure after treatment with non-steroidal anti-inflammatory drugs. Eur. J. Pediatr. 163, 148–150.
Ushida, K., Hatanaka, H., Inoue, R., Tsukahara, T., Phillips, G.O., 2011. Effect of long term ingestion of gum Arabic on the adipose tissues of female mice. Food Hydrocolloids 25, 1344–1349.
Viedt, C., Dechend, R., Fei, J., Hänsch, G.M., Kreuzer, J., Orth, S.R., 2002. MCP-1 induces inflammatory activation of human tubular epithelial cells: involvement of the transcription factors, nuclear factor-κB and activating protein-1. J. Am. Soc. Nephrol. 13, 1534–1547.
Vielhauer, V., Berning, E., Eis, V., Kretzler, M., Segerer, S., Strutz, F., Horuk, R., Gröne, H.J., Schlöndorff, D., Anders, H.J., 2004. CCR1 blockade reduces interstitial inflammation and fibrosis in mice with glomerulosclerosis and nephrotic syndrome. Kidney Int. 66, 2264–2278.
Vieyra, M.B., Heeger, P.S., 2010. Novel aspects of complement in kidney injury. Kidney Int. 77, 495–499.
Xuan, N.T., Shumilina, E., Nasir, O., Bobbala, D., Gotz, F., Lang, F., 2010. Stimulation of mouse dendritic cells by Gum Arabic. Cell. Physiol. Biochem. 25, 641–648.
Yamate, J., Tatsumi, M., Nakatsuji, S., Kuwamura, M., Kotani, T., Sakuma, S., 1995. Immunohistochemical observations on the kinetics of macrophages and myofibroblasts in rat renal interstitial fibrosis induced by cis–diamminedichloroplatinum. J. Comp. Pathol. 112, 27–39.