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التأثيرات البيولوجية المحتملة للصمغ العربي على اضطرابات الكلى التي يسببها الأرجينين في الجرذان

Potential biological effects of gum Arabic on kidney disorders induced by arginine in rats

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التأثيرات البيولوجية المحتملة للصمغ العربى على إعتلالات الكلى فى الفئران المستحث بالأرجينين

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المستخلص:

صممت هذه الدراسة لمعرفة التأثيرات البيولوجية للصمغ العربي (GA) على اعتلالات الكلى التي يسببها الأرجينين في الفئران . أيضا، إضافة الصمغ العربى إلى نظام غذائي منخفض البروتين يعد واحد من اهم علاجات اعتلالات الكلى بالإضافة الى التاثيرات البيولوجية الإيجابية المحتملة للصمغ العربى على مرضى الكلى سيكون هدف هذه الدراسة . أظهرت البيانات التي تم الحصول عليها أن متوسط قيمة حمض اليوريك والكرياتينين من مجموعة التحكم السلبية التي تم تغذيتها على النظام الغذائي القاعدي كان ١.٧٣ و ٠،٨٠ مجم-dl1 ، بينما حمض البوليك والكرياتينين من المجموعة التي تم تغذيتها على BD تحتوي على ٢٪ أرجينين (Control + ve) كان ٢.٩١ و ١.٧٩ مجم-dl 1على التوالي. كان معدل الزيادة في حمض اليوريك والكرياتينين نتيجة اعتلالات الكلى ٦٨.٢٨ و ١٢٤.١٥٪. المجموعات الاضافية التي تتغذى على GA ونظام غذائي منخفض البروتين (LPD) يحتوي على ٢٪ أرجينين أدى إلى انخفاض حمض البوليك والكرياتينين بمعدلات مختلفة. كما أظهرت مجموعة المعالجة التي تم تغذيتها على GA و LPD تأثيرًا فعال حيث سجلت أعلى معدل تناقص في حمض اليوريك والكرياتينين (-١٩.٩٩ و -٢١.١٥٪ على التوالي). أيضا ، تم تسجيل نفس المعدل في محتوى المعادن في الدم (Na و K, ومحتوى malondialdehyde (MDA) والمؤشرات الحيوية للإجهاد التأكسدي والالتهاب في الجسم. يوصى بمزيد من الاهتمام في المستقبل لإجراء المزيد من الأبحاث في مجال GA وتوسعة تطبيقاتها في الأنظمة الغذائية البشرية والتطبيقات الصناعية والطبية مثل مرضى أمراض الكلى بدلاً من الأدوية / المواد الكيميائية المستخدمة التي تتسبب في إحداث مخاطر صحية وآثار جانبية عالية للإنسان.

الكلمات المفتاحية:

الصمغ العربي (GA) – اعتلالات الكلى – الأرجينين – المؤشرات الحيوية للإجهاد التأكسدي والالتهاب في الجسم – نظام غذائي منخفض البروتين.

Potential biological effects of gum Arabic on kidney disorders induced by arginine in rats

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Abstract:

Several decades ago, hude studies reported that recent pharmacological therapy is costly and associated with multiple side effects resulting in patient non-compliance. Therefore, there is a great need to search for alternative therapies particularly from natural sources as these are cost effective and possess minimal side effects. The present study will designe to explore the biological effects of gum arabic (GA) on kidney disorders induced by arginine in rats. Also, the addition of GA to low protein diet (LPD), one of an important kidney disorders treatment, in a trial to add some positive biological effects to the kidney patients will be in the scope of this study. The obtained data revealed that The mean value of uric acid and creatinine of the negative control group fed on basal diet was 1.73 and 0,80 $mg.dl^{-1}$, while uric acid and creatinine of group fed on BD containing 2% arginine (Control +ve) was 2.91 and 1.79 $mg.dl^{-1}$, respectively. The rate of increasing in uric acid and creatinine as the result of kidney disorders induction was 68.28 and 124.15**%.** Additional of groups fed on GA and low protein diet (LPD) containing 2% arginine and led to decrease uric acid and creatinine by different rates. Co-treatment group fed on GA and LPD exhibited synergistic effect and recorded the highest decreasing rate in uric acid and creatinine (-19.99 and -21.15%, respectively). Also, the same behavior was recorded for serum mineral content (Na and K) and malondialdehyde content (MDA), the biomarkers of oxidative stress and inflammation in the body**.** In conclusion, we recommended to pay more attention in the future to carry out more research in the area of GA and extended its applications in human diets, industrial and medical applications such kidney diseases patients instead of the drugs/chemicals used which have induced healthy hazards, side effects and high coast for the human being.

Keywords: Gum Arabic (GA) - kidney disorders – arginine - malondialdehyde content (MDA) - low protein diet (LPD).

Introduction

Several decades ago, hude studies reported that recent pharmacological therapy is costly and associated with multiple side effects resulting in patient non-compliance. Therefore, there is a great need to search for alternative therapies particularly from natural sources as these are cost effective and possess minimal side effects. Recently, many , universities, authorites and research centers pay more attention towordes the using of gum Arabic (GA) as an alternative therapy. GA is an edible biopolymer obtained as exudates of mature trees of *Acacia Senegal* and *Acacia seyal* which grow principally in the African region of Sahe in Sudan. The exudate is a non-viscous liquid, rich in soluble fibers, and its emanation from the stems and branches usually occurs under stress conditions such as drought, poor soil fertility, and injury (Williams and Phillips, 2000). Such as reported by MSN (2008) there are close to 900 *Acacia* species capable of producing gum. These are primarily located in tropical climates, with about 130 of them located specifically on the African continent. Africa, therefore, quickly became the major site of the production of gum; this is the reason why it is also referred to as 'Senegal Gum'. Gum is essentially the secretion of several acacia (leguminous) trees. Acacia Gum species, of which there are up to seventeen, produce acacia gum of varying quality and quantity. Interestingly, close to 80% of Gum Arabic is produced by the *Acacia senegal* (in Sudan). The remainder is produced either by the *Acacia laeta* or the *Acacia seyal*, with each species contributing 10% to the total supply of gum. The gum produced by the *Acacia Senegal* is commonly referred to as "hard gum" and the gum from *Acacia seyal*, as "flaky gum".

Several years ago, the effective biological roles of GA has been confirmed including reduction in plasma cholesterol level in animals and humans (Sharma, 1985 and Tiss *et al.*, 2001), anticarcinogenic effect (Nasir *et al.*, 2010) and antioxidant effect (Al-Majed *et al.*, 2002; Ali *et al.*, 2003; Trommer and Neubert, 2005; Ali and AlMoundhri, 2006 and Hegazy, 2014) with a protective role against hepatic and cardiac toxicities. In addition to that, it has been claimed that GA alleviates effects of chronic renal failure in humans (Ali *et al.*, 2008; Glover *et al.*, 2009 and Ali *et al.*, 2010). Also, GA is indigestible to both humans and animals, not degraded in the intestine, but fermented in the colon to give short-chain fatty acids, leading to a large range of possible health benefits (Phillips and Philips, 2011). One of these benefits is its prebiotic effect (Phillips *et al.*, 2007). Calame *et al.*, (2008) reported that four week supplementation with Gum Arabic (10 g/day) led to significant increases in Bifidobacteria, Lactobacteria, and Bacteriodes indicating a prebiotic effect. Several epidemiological studies suggest that a high intake of dietary fiber, including GA (dietary fiber > 80%), is associated

with beneficial effects on fat metabolism (Slavin, 2003 and Ali *et al.,* 2009). It can serve to reduce obesity and therefore prevent associated complications in humans including coronary heart disease, stroke and diabetes (Lear et *al.,* 2003). So, GA has been widely used around the world in folk medicine. It has been reported to be used internally for the treatment of inflammation of the intestinal mucosa, and externally to cover inflamed surfaces (Gamal el-din *et al.,* 2003). Despite the fact that GA is widely used as a vehicle for drugs in experimental physiological and pharmacological experiments, and is assumed to be an ‘‘inert” substance, some recent reports have claimed that GA possesses anti-oxidant, nephroprotect ant and other effects (Gamal el-din *et al.,* 2003 and Ali *et al.,* 2008). Clinically, it has been tried in patients with chronic renal failure, and it was claimed that it helps reduce urea and creatinine plasma concentrations and reduces the need for dialysis from 3 to 2 times per week (Suliman *et al.,* 2000).

Kidney disease is associated with many kinds of metabolic changes caused by the kidney disease and also attributable to dialysis treatment. Phenomena such as accumulation or deficit of various substances and dysregulation of metabolic pathways combine in the pathogenesis of these changes (Cibulka *et al.* 2005). All of these factors and others lead to many serious complications for CKD patients during the course of predialysis and dialysis. All accelerate the development of atherosclerosis, malnutrition inflammation complex syndrome (MICS), anemia, hyperparathyroidism, and other serious problems that markedly affect prognosis and the quality of life of patients with CKF (Lindner *et al.* 1974, Durak *et al.* 1994, Silver 2000, Cibulka *et al.* 2005). As patients progress through the stages of CKD, nutritional requirements are altered and metabolism of protein, water, salt, potassium, and phosphorus are affected (Appel *et al.,* 1985). These changes lead to ineffective energy generation despite adequate intake of protein and carbohydrate substrates. CKF patients from the National Institutes of Health (NIH)-sponsored Modification of Diet in Renal Disease (MDRD) study who were assigned to low-protein diets also maintained acceptable nutritional parameters (Kopple et al., 1997). Protein restriction has been shown to decrease the degree of proteinuria (Kaysen *et al.,* 1986; and Aparicio *et al.,* 1988) and it can suppress proteinuria synergistically with angiotensin-converting enzyme inhibitors (ACEi). Protein-restricted diets have also been shown to reduce intrarenal and systemic hypertension (Bellizzi et al., 2007). Further studies delineating the effects of protein restriction on the progression of CKD are warranted. Regardless of the limitations of the MDRD study and other reports, we conclude that the benefit of a low-protein diet on the progression of kidney failure is not yet proved. So, the present study will design to explore the effect of low protein diet (LPD) on nutritional issues of

rats suffering from chronic kidney disease Also, kidney diseases such CKD is an associated with mineral metabolism and bone disorders'' comprises abnormalities in bone and mineral metabolism and/or extra skeletal calcification secondary to CKD pathophysiology (Gal-Moscovici and Sprague, 2007).

Regardless of the limitations of the Modification of Diet in Renal Disease (MDRD) study, the present study will design to explore the biological effects of gum arabic (GA) on kidney disorders induced by arginine in rats. Also, the addition of GA to low protein diet (LPD), one of an important kidney disorders treatment, in a trial to add some positive biological effects to the kidney patients will be in the scope of this study.

Materials and methods

Materials

Gum Arabic (*Acacia senegal* L.) was obtained in three batches from the SAVANNA Companies Group (Processing Gums, Juices and Confectionery), Khartoum, Sudan. (Specification: appearance colour- off white, appearance form- powder, purity, 98.65± 0.45%). Arginine, analytical grade, used for induction of chronic kidney disease (CKD) among rats was purchased from Sigma Chemical Co. (St. Louis, MO, USA). Casein was obtained from Morgan Chemical Co., Cairo, Egypt. The rest of chemicals, reagents and solvents were of analytical grade and purchased from El-Ghomhorya Co. for Trading Drugs, Chemicals and Medical Instruments. Cairo, Egypt.

Animals

Animals used in this study, adult male albino rats (140-150 g per each) were obtained from Research Institute of Ophthalmology, Medical Analysis Department, Giza, Egypt.

Basal and specific diets

The basic and specific diets were prepared such as mentioned by AIN, (1993) and Kusano *et al.,* (2008), Table (A). The used vitamin mixture component (Table B) was that recommended by (Campbell, 1963) while the salt mixture (Table C) used was formulated according to (Hegsted, 1941).

Experimental design:

All biological experiments performed complied with the rulings of the Institute of Laboratory Animal Resources, Commission on life Sciences, National Research Council (**NRC, 1996**). Rats (n=35 rats), 140-150g per each, were housed individually in wire cages in a room maintained at 25 ± 2 ^{0}C and kept under normal healthy conditions. All rats were fed on basal diet for one-week before starting the experiment for acclimatization. After one

week period, the rats were divided into two main groups, the first group [Group 1, 5 rats, Basal diet (BD), Control-ve] still fed on basal diet and the other main group (40 rats) fed on basal diet plus 2 %arginine to induce chronic kidney disease (CKD) according to ***Yokozawa et al., (2003)*** then classified into eight sub groups as follow:

Group (2): Basal diet (BD) + 2% arginine (Control +ve)
Group (3): BD + 2% arginine + 2% gum arabic (GA)
Group (4): BD + 2% arginine + 3% gum arabic (GA)
Group (5): Low protein diet (LPD) + 2% arginine
Group (6): LPD + 2% arginine + 2% GA
Group (8): LPD + 2% arginine + 3% GA

Table (1). Formulae of the diets used in this study

Components	Basal diet (BD)	Low protein diet (LPD)
Protein (%)	12.6	8.4
Phosphorus (%)	0.5	0.5
Potassium (%)	0.5	0.5
Casein	15	10
KH_2PO_4	1.014	1.014
Sucrose	10	10
Corn oil	7.0	7.0
Cellulose	5.0	5.0
Mineral mix	3.5	3.5
Vitamin mix	1.0	1.0
Methionine	0.3	0.3
Choline chloride	0.25	0.25
Starch	56.94	61.94

During the condition period and throughout the trial, food and tap water were provided and ad libitum. Rats were weighed twice weekly; feed intake (FI) and body weight gain (BWG) were calculated. During the experiment period (28 days), the quantities of diet, which were consumed and/or wasted, were recorded every day. In addition, rat's weight was recorded weekly, to determine food intake and body weight gain % according to Chapman *et al.*, (1959). BWG was determined using the follow equation:

$$\text{Body weight gain (\%)} = \frac{\text{Final weight (g)} - \text{initial weight (g)}}{\text{Initial weight (g)}} \times 100$$

Blood sampling

At the end of experiment period, 28 days, blood samples were collected after 12 hours fasting using the abdominal aorta and rats were scarified under ether anesthetized. Blood samples were withdrawn from the

antecubital vein into glass centrifuge tubes, containing oxalate solution (1.34 %) as anticoagulant. After centrifugation at 3000 rpm for 10 min., plasma was with drown and used for the analysis of blood lipid parameters. The erythrocyte residue was washed with three successive portions of sodium chloride solution (0.9 %) and then haemolysed with deionised water for 30 min. Haemolysate was then centrifuged at 30,000 rpm for 30 min. and the supernatant fractions was transferred to a clean test tube and analyzed of antioxidant enzymes (Stroev and Makarova, 1989).

Hematological analysis

Kidney functions

Creatinine

Serum creatinine concentration was determined using the modified kinetic method of Young *et al.*, (1975) by using kit supplied by Biocon Company.

Urea

Serum urea concentration was determined by Chaney *et al.*, (1962) by using kit supplied by Biocon Company.

Sodium and potassium content

Sodium (Na) and potassium (K) content in plasma samples were determined by the adaptation the method mentioned by Singh *et al*., (1991). One hundred µl of plasma sample were transferred into a digested glass tube and 2 ml of tri-acids mixture (containing nitric acid: perchloric acid : sulfuric acid in the ratio of 20 : 4 : 1 v/v respectively) were added to each tube. The tubes content were digested gradually as follow, 30 min at 70 ^{0}C; 30 min at 180 ^{0}C and 30 min at 220 ^{0}C. After digestion, the mixture was cooled, dissolved in MilliQ water, and the volume was increased to 10 ml in volumetric beaker. After filtration in ashless filter paper, aliquots were analyzed for Na and K content using of atomic absorption spectrophotometer, type Perkin - Elmer, Model 2380.

Malonaldialdehyde content (MDA)

Malonaldialdehyde content (MDA) content was measured as thiobarbituric acid reactive substances (TBARS) as described by Buege and Aust, (1978). Half milliliter of plasma were added to 1.0 ml of thiobarbituric acid reagent, consisting of 15% TCA, 0.375% thiobarbituric acid (TBA) and 0.01% butylated hydroxytoluene in 0.25 N HCl. Twenty-five microliters of 0.1 M $FeSO_4.7H_2O$ was added and the mixture was heated for 20 min in boiling water. The samples were centrifuged at 1000 rpm for 10 min and the absorbance was read at 535 nm using Labo-med. Inc., spectrophotometer

against a reagent blank. The absorbance of the samples was compared to a standard curve of known concentrations of malonaldehyde.

Statistical Analysis

All measurements were done in triplicate and recorded as mean±SD. Statistical analysis was performed with the Student *t*-test and MINITAB 12 computer program (Minitab Inc., State College, PA).

Results and Discussion

Effect of gum Arabic (GA) and low protein diet (LPD) on Food intake (FI) and Body weight gain (BWG) of rats suffering from kidney disorders induced by arginine.

Data presented in Table (2) showed Effect of gum Arabic (GA) and low protein diet (LPD) on serum food intake (FI) and body weight gain (BWG) of rats suffering from kidney disease induced by arginine. From such data it could be noticed that the mean value of FI was decreased in positive group fed on diet containing 2% arginine as compared to normal group fed on basal diet (BD, Control -ve). The mean value of FI of the negative control group fed on basal diet was 17.53 (g/day for each rat), while food intake of group fed on BD containing 2% arginine (Control +ve) was 13,47 (g/day for each rat). The rate of decreasing in FI as the result of kidney disorders induction was -23.15**%.** Additional of groups fed on GA and low protein diet (LPD) containing 2% arginine and led to increase in FI by different rates . Co-treatment group fed on GA and LPD exhibited synergistic effect and recorded the highest increasing rate in food intake (15.74%).

Regarding body weight gain (BWG), data it indicated that the mean value of BWG was decreased in positive group fed on diet containing 2% arginine as compared to normal group fed on basal diet (BD, Control -ve). The mean value of BWG of the negative control group fed on basal diet was 28.34 while BWG of group fed on BD containing 2% arginine (Control +ve) was 11.65 (g/day for each rat). The rate of decreasing in BWG as the result of kidney disorders induction was -59.32**%.** Additional of groups fed on GA and low protein diet (LPD) containing 2% arginine and led to increase in BWG by different rates . Co-treatment group fed on GA and LPD exhibited synergistic effect and recorded the highest increasing rate in food intake (65.06%).

Table 2. Effect of gum Arabic (GA) and low protein diet (LPD) on serum food intake (FI) and body weight gain (BWG) of rats suffering from kidney disorders induced by arginine

Groups	FI ($g.day^{-1}$)		BWG (%)	
	Mean ±SD	% of change	Mean ±SD	% of change
Basal diet (BD, Control -ve)	17.53 ± 1.11 ^{a}	0.00	28.64 ± 2.14 ^{a}	0.00
BD + 2% arginine (Control +ve)	13.47 ± 0.66 ^{c}	-23.15	11.65 ± 2.03 ^{e}	-59.32
BD + 2% arginine + 2% GA	14.30 ± 2.01 ^{b}	6.13	13.51 ± 1.55 ^{cd}	15.97
BD + 2% arginine +3% GA	14.40 ± 1.14 ^{b}	6.87	14.01 ± 1.67 ^{cd}	20.26
LPD + 2% arginine	14.68 ± 0.56 ^{b}	8.95	15.82 ± 0.78 ^{c}	35.79
LPD + 2% arginine + 2% GA	15.12 ± 2.31 ^{b}	12.22	16.39 ± 1.21 ^{c}	40.69
LPD + 2% arginine + 3% GA	15.74 ± 1.23 ^{b}	16.82	19.23 ± 0.76 ^{b}	65.06

Means values with the different superscript letters in the same column means significantly different at $p \leq 0.05$

The present data are in accordance with the obtained by El-Agooze, (2015) who studies the effect of low phosphorus & potassium diet (LPPD), low protein diet (LPD) and gum Arabic (GA) on nutritional issues of rats suffering from chronic kidney disease. Also, Kowale and Misra (1976) indicated that fed groups of young rats on a diet with 5, 10 or 20% casein or chick pea protein, the food intake and body weights were measured regularly after 6 or 12 weeks. They also showed that the rats lost weight with low concentration of chick pea but at 20% protein level the weight gain was similar with both casein and chick pea. On the other hand, Adelman and Holliday (1977) reported that reduction of renal function resulted in a marked reduction of food intake and weight gain. Also, rats fed diet containing 21% casein had a significantly reduced length of life compared with rats fed the 16.6% casein diet (Maeda *et al.*, 1985). Furthermore, Parrish (2004) and Ammar (2011) concluded that chronic renal failure (CRF) is associated with loss of body mass which improved with the using of low protein diet and gum Arabic.

Effect of gum Arabic (GA) and low protein diet (LPD) on serum minerals of rats suffering from kidney disorders induced by arginine

Data presented in Table (3) showed Effect of gum Arabic (GA) and low protein diet (LPD) on serum sodium (Na) and potassium (K) of rats suffering from kidney disease induced by arginine. From such data it could be noticed that the mean value of Na and K were increased in positive group fed on diet containing 2% arginine as compared to normal group fed on basal diet (BD, Control -ve). The mean value of Na and K of the negative control group fed on basal diet was 111.23 and 3.39 $mmol.l^{-1}$, while Na and K of group fed on BD containing 2% arginine (Control +ve) was 165.62 and 5.25

mmol.l^{-1} , respectively. The rate of decreasing in NA and K as the result of kidney disorders induction was 48.90 and 54.94**%.** Additional of groups fed on GA and low protein diet (LPD) containing 2% arginine and led to decrease Na and K by different rates . Co-treatment group fed on GA and LPD exhibited synergistic effect and recorded the highest decreasing rate in Na and K (-23.22 and -32.57%, respectively).

Table 3. Effect of low protein diet (LPD) and gum Arabic (GA) on serum sodium and potassium levels of rats suffering from chronic kidney disease

Groups	Sodium (mmol.l^{-1})		Potassium (mmol.l^{-1})	
	Mean ±SD	% of change	Mean ±SD	% of change
Basal diet (BD, Control -ve)	111.23 ± 13.4 ^{e}	------	3.39 ± 0.32 ^{d}	------
BD + 2% arginine (Control +ve)	165.62 ± 14.8 ^{a}	48.90	5.25 ± 0.26 ^{a}	54.94
BD + 2% arginine + 2% GA	155.68 ± 10.67 ^{b}	-6.00	4.55 ± 0.51 ^{b}	-13.32
BD + 2% arginine +3% GA	146.23 ± 8.10 ^{c}	-11.71	4.21 ± 1.03 ^{b}	-19.81
LPD + 2% arginine	141.16 ± 9.50 ^{c}	-14.77	4.19 ± 1.21 ^{b}	-20.19
LPD + 2% arginine + 2% GA	136.47 ± 12.54 ^{c}	-17.60	3.93 ± 0.71 ^{bc}	-25.18
LPD + 2% arginine + 3% GA	127.16 ± 10.32 ^{d}	-23.22	3.54 ± 0.27 ^{bc}	-32.57

Means values with the different superscript letters in the same column means significantly different at p≤0.05

Such as mentioned by Appel *et al.,* (1985), as patients progress through the stages of chronic kidney disease, nutritional requirements are altered and metabolism of protein, water, salt, potassium, and phosphorus are affected. These changes lead to ineffective energy generation despite adequate intake of protein and carbohydrate substrates. In more extreme manifestations, these alterations in nutrient use cause ‘‘uremic malnutrition,’’ a syndrome that is distinct from malnutrition caused by inadequate nutrient intake. Both inadequate nutrient intake and ineffective nutrient use can contribute to nutritional disorders in chronic kidney disease patients (Robert *et al.,* 2008). In similar study, Ammar *(2011)* reported that the best results of serum Na and K recorded for the group fed on low protein (LPD), phosphorus and potassium diet (PPD) and treated daily with 15% gum Arabic. These treatments decreased serum sodium and potassium by about 9.72 and 26.11% for LPD and 9.26 and 20.94% for PPD, respectively, as compared to the positive control group. In related to this issue, Fila *et al (2011)* was studied the nephrotic syndrome features massive proteinuria and retention of sodium which promotes ascites formation. In the puromycin aminonucleoside-induced rat model of nephrotic syndrome, sodium retention originates from the collecting duct where it generates a driving force for potassium secretion. They reported that nephrotic patients were found to display plasma potassium

levels in the normal to high range and recommend not only a low sodium diet but also a controlled potassium diet for patients with nephrotic syndrome. The present data are in accordance with the obtained by El-Agooze, (2015) who studies the effect of low phosphorus & potassium diet (LPPD), low protein diet (LPD) and gum Arabic (GA) on serum minerals of rats suffering from chronic kidney disease.

Effect of low protein diet (LPD) and gum Arabic (GA) on kidney functions of rats suffering from chronic kidney disorders induced by arginine

Data presented in Table (4) showed Effect of gum Arabic (GA) and low protein diet (LPD) on serum uric acid and creatinine of rats suffering from kidney disease induced by arginine. From such data it could be noticed that the mean value of uric acid and creatinine were increased in positive group fed on diet containing 2% arginine as compared to normal group fed on basal diet (BD, Control -ve). The mean value of uric acid and creatinine of the negative control group fed on basal diet was 1.73 and 0,80 $mg.dl^{-1}$, while uric acid and creatinine of group fed on BD containing 2% arginine (Control +ve) was 2.91 and 1.79 $mg.dl^{-1}$, respectively. The rate of increasing in uric acid and creatinine as the result of kidney disorders induction was 68.28 and 124.15%. Additional of groups fed on GA and low protein diet (LPD) containing 2% arginine and led to decrease Na and K by different rates . Co-treatment group fed on GA and LPD exhibited synergistic effect and recorded the highest decreasing rate in uric acid and creatinine (-19.99 and -21.15%, respectively).

Urea is formed in the liver as the end product of protein metabolism. During ingestion, protein is broke down into amino acids. In the liver, these amino acids are catabolized and free ammonia is formed. The ammonia is combined to form urea (Pagana and pagana, 1997). Urea, the major product of protein catabolism measuring urea is the most popular laboratory procedure for assessing renal functions (Bennett *et al*., 1995). Creatinine is a catabolic product of creatine phosphate, which is used in skeletal muscle concentration. In the skeletal muscle serum creatinine levels are elevated by renal disease and dehydration (Pagana and pagana, 1997). In the current work, the tested diets such LPD and GA be more efficient for reducing serum level of urea and creatinine, the biomarkers of kidney functions stress induced by chronic kidney diseases. Such data are in accordance with that obtained by Barsotti *et al (1996)* who reported that the nutritional treatment of chronic kidney diseases with conventional low-protein diet. It is effective in reducing uremic intoxication, slowing the progression of renal failure and preventing secondary hyperparathyroidism. Also, Ammar (2011*)* reported

that the best results of serum uric and creatinine recorded for the group fed on low protein (LPD) and treated daily with 15% GA.

Table 4. Effect of low protein diet (LPD) and gum Arabic (GA) on kidney functions of rats suffering from chronic kidney disorders induced by arginine

Groups	Uric acid ($mg.dl^{-1}$)		Creatinine ($mg.dl^{-1}$)	
	Mean ±SD	% of change	Mean ±SD	% of change
Basal diet (BD, Control -ve)	1.73 ± 0.34^{c}	0.00	0.80 ± 0.13^{c}	0.00
BD + 2% arginine (Control +ve)	2.91 ± 0.13^{a}	68.24	1.79 ± 0.34^{a}	124.15
BD + 2% arginine + 2% GA	2.81 ± 0.30^{a}	-3.38	1.70 ± 0.16^{a}	-5.20
BD + 2% arginine +3% GA	2.73 ± 0.23^{a}	-6.05	1.58 ± 0.33^{a}	-12.03
LPD + 2% arginine	2.70 ± 0.44^{ab}	-7.11	1.51 ± 0.17^{a}	-15.97
LPD + 2% arginine + 2% GA	2.42 ± 0.56^{b}	-16.78	1.49 ± 0.16^{ab}	-17.12
LPD + 2% arginine + 3% GA	2.33 ± 0.11^{b}	-19.99	1.41 ± 0.25^{b}	-21.15

Means values with the different superscript letters in the same column means significantly different at $p \leq 0.05$

The benefits of low protein diets for patients with chronic kidney diseases were established over 100 years ago. For example, In 1869, Beale and colleagues showed that the uraemic symptoms in patients with kidney failure were ameliorated by reducing foods rich in protein. The benefits of dietary protein restriction are multifactorial. First, restricting protein in the diet provides favourable metabolic parameters. The typical biochemical profile (acidaemia, hypophosphatemia, azotaemia) seen in chronic kidney disease patients who receive minimal attention to their diet is not typically seen when proper dietary counseling is emphasized. Moreover, low protein diets have been shown to improve insulin resistance and osteodystrophy (Frohling *et al*., 1983 and Gin *et al*., 1994). Patients with chronic kidney disease (with an average glomular filtration rate of 18 ml/min) were given a low protein diets along with amino acid analogue supplements, and were found to maintain a neutral nitrogen balance without the development of acidaemia or hyperphosphataemia (Tom *et al.,* 1995). Patients from the National Institutes of Health -sponsored Modification of Diet in Renal Disease (MDRD) studies who were assigned to low-protein diets also maintained acceptable nutritional parameters (Kopple *et al.*, 1997). A study by Bellizzi and colleagues revealed that proteinrestricted diets are associated with improved blood pressure control. They evaluated chronic kidneys disease patients (average glomular filtration rate <20ml/min) who were given a low-protein diet supplemented with ketoanalogs of amino acids and found a

significant decrease in mean blood pressure (103±11– 95±7 mmHg) over six months compared with controls. There was also a decrease in the average number of antihypertensive medications used (Bellizzi *et al.,* 2007). We emphasise the importance of these data, given the detrimental effect of hypertension on the progression of chronic kidney disease. Second, protein-restricted diets generally improve uraemic symptoms and, therefore, offer the possibility of delaying initiation of renal replacement therapy (Kopple *et al.*, 1997). This occurs because most uraemic symptoms are dependent on the accumulation of nitrogenous waste products and correlated with SUN, and these problems can be limited by protein restriction. Walser and Hill showed in a study of patients with end-stage kidney disease (glomular filtration rate <10ml/min in non-diabetics and <15ml/min in diabetics) were safely managed with a supplemented low-protein diet for a median of one year before the initiation of dialysis therapy (Walser and Hill, 1999).

On the other side, the effect of GA on kidney functions, Bliss *et al.* (1996) investigated that supplementation with GA fiber increases fecal nitrogen excretion and lowers serum urea nitrogen concentration in chronic renal failure patients consuming a low-protein diet. The addition of GA to the diet induced a 20 to 30% decrease in blood urea and renal nitrogen excretion relative to the control, indicating a potential for GA diet therapy in chronic renal disease (Younes *et al.*, 1999). GA supplementation of a low-protein diet in children with end-stage renal disease have been studied by Al-Mosawi *(2004)* and found that dietary supplementation with acacia gum may be an alternative to renal replacement therapy to improve the quality of life and reduce or eliminate the need for dialysis in children. The effect of GA oral treatment on the metabolic profile of chronic renal failure patients was studied by Ali *et al., (2008)* and found that, serum uric acid, urea nitrogen and creatinine showed significantly decreased in the groups of GA and conclude that oral administration of GA could conceivably alleviate adverse effects of chronic kidney disease. Also, *Badreldin et al. (2008)* mentioned that GA is a branched-chain, complex polysaccharide, either neutral or slightly acidic, found as mixed Ca, Mg and K salt of a polysaccharidic acid. The backbone is composed of 1, 3-linked β-d-galactopyranosyl units. The side chains are composed of two to five 1, 3-linked β-D-galactopyranosyl units, joined to the main chain by 1, 6-linkages. Pharmacologically, GA has been claimed to act as an antioxidant, and to protect against experimental hepatic-, renal- and cardiac toxicities in rats. GA has been claimed to alleviate the adverse effects of chronic renal failure in humans. Finally, El-Agooze, (2015) studied the effect of low phosphorus & potassium diet, low protein diet and GA on serum kidneys functions parameters of rats suffering

from chronic kidney disease. Their data are accordance with that obtained by the present study.

Effect of low protein diet (LPD) and gum Arabic (GA) on oxidative stress (malondialdehyde content, MDA) of rats suffering from chronic kidney disease induced by arginine

Data presented in Table (5) showed the effect of gum Arabic (GA) and low protein diet (LPD) on oxidative stress (malondialdehyde content, MDA) of rats suffering from chronic kidney disease induced by arginine. From such data it could be noticed that the mean value of MDA was increased in positive group fed on diet containing 2% arginine as compared to normal group fed on basal diet (BD, Control -ve). The mean value of MDA of the negative control group fed on basal diet was 2.94 $nmol.mg^{-1}$ tissue protein, while MDA of group fed on BD containing 2% arginine (Control +ve) was 4.37 $nmol.mg^{-1}$ tissue protein, respectively. The rate of decreasing in MDA as the result of kidney disorders induction was 48.64**%.** Additional of groups fed on GA and low protein diet (LPD) containing 2% arginine and led to decrease MDA by different rates . Co-treatment group fed on GA and LPD exhibited synergistic effect and recorded the highest decreasing rate in Na and K (-21.05%, respectively).

Table 5. Effect of low protein diet (LPD) and gum Arabic (GA) on malondialdehyde content (MDA) of rats suffering from chronic kidney disease

Groups	MDA ($nmol.mg^{-1}$ tissue protein)	
	Mean ±SD	% of change
Basal diet (BD, Control -ve)	2.94 ± 0.32 ^{c}	-----
BD + 2% arginine (Control +ve)	4.37 ± 1.02^{a}	48.64
BD + 2% arginine + 2% GA	3.97 ± 0.11 ^{a}	-9.15
BD + 2% arginine +3% GA	3.76 ± 0.54 ^{ab}	-13.96
LPD + 2% arginine	3.77 ± 0.61 ^{ab}	-13.73
LPD + 2% arginine + 2% GA	3.70 ± 0.33 ^{ab}	-15.33
LPD + 2% arginine + 3% GA	3.45 ± 0.24 ^{b}	-21.05

Means values with the different superscript letters in the same column means significantly different at $p \leq 0.05$

According to our knowledge, data regarding the MDA content of chronic kidney disease rats feeding with LPD and GA was the first time. Therefore, it makes the comparison and interpretation of the present data is partially hard. Clinical evidences for different disease-associated oxidative stress (OS) have been provided by measurement of either biomarkers or end-

products of free radical-mediated oxidative processes (Elhassaneen and Salem, 2014, Sayed Ahmed, 2016; El-Harbi, 2018 and Magran *et al.*, 2018). For instance, lipid peroxidation markers such as malondialdehyde (MDA), one of the most important compounds in TBARS and major products of the oxidation of polyunsaturated fatty acids,, lipid hydroperoxides and conjugated dienes are found to be increased in plasma from obese subjects in many clinical studies (Vincent and Taylor, 2006). Systemic metabolic alterations associated with diseases contribute to the increase in OS have been reported by many authors. For example, hyperglycemia as a hallmark of type II diabetes, a metabolic complication of obesity, induces oxidative stress through activation of the polyol and hexosamine pathways, production of advanced glycation end-products (AGE), and increase of diacylglycerols (DAG) synthesis (DCCTRG, 1993 and Le Lay *et al.*, 2014). Excess of circulating lipids induces ROS formation pathways, which contribute to the increase in lipid oxidation and protein carbonylation (Jensen *et al.*, 1989). Leptin and angiotensin II, secreted at high levels by adipocytes, are inducers of ROS generation and might therefore promote inflammation and lipid peroxidation (Bouloumie *et al.*, 1999).

Long time ago, interest in the possible significance of MDA on human health has been stimulated by reports that are mutagenic and carcinogenic compound (Shamberger *et al*., 1974). The positive effects of GA on oxidants formation/ concentration of chronic kidney disease rats could be attributed to several mechanisms induced by their bioactive components content (phenolic acide, polysaccharides etc. In this context, Coskun *et al.*, (2005) found that phenolics such as found in GA extract, have anti-oxidative and anti-inflammatory activities. Such dietary phenolics found in GA are metabolized in liver, inhibiting liver injury induced by diabetes i.e. enhancing lipid metabolism, reducing OS may be particularly effective, consequently. Additionally, the co-treatment gave maximum reduction yield of plasma MDA when compared with the individual treatment. It could be mean that a combination of different diets may be more efficient for reducing plasma MDA level, the biomarkers of oxidative stress and inflammation in the body, because the interactive effects occurred by different treatment tested.

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