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Gum Arabic in renal disease (GARDS Study): Clinical evidence of dietary supplementation impact on progression of renal dysfunction

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ABSTRACT

Administration of Gum Arabic (GA) was associated with an increase in estimated Glomerular filtration rate (eGFR) at three months (pre 24.64 ± 8.89 vs 26.20 ± 10.1p = 0.02). Subsequently there was no significant fall in eGFR. This translated to positive change in Δ eGFR within quarter at three months, (Δ eGFR 4.89 ml/min/year p=<0.001 vs pre) and six months (Δ eGFR 0.79 ml/min/year, p < 0.001 vs pre) compared to pre-intervention values. At 9 and 12 months although the mean Δ eGFR in quarter was negative, this rate of decline in renal function remained significantly less than prior to intervention (9 months Δ eGFR −1.27 ml/min/year, p= <0.001 vs pre, 12 months delta Δ eGFR −1.54 ml/min/year, p < 0.001 vs pre). Similarly, mean reciprocal creatinine, declined by 11% in the pre-intervention period but was no different to the pre-intervention values for the duration of intervention. In conclusion oral administration of Gum Arabic attenuates the rate of decline in renal function.

1. Introduction

It is widely accepted that a high intake of dietary fibre is associated with numerous health benefits, with reduced mortality documented in those consuming a diet rich in whole grain (Jacobs, Meyer, & Solvoll, 2001). In patients with chronic kidney disease (CKD), prevention of hyperkalaemia is often associated with dietary advice limiting the intake of fruits and vegetables. As a result it is well established that the dietary fibre intake of patients with CKD is far below the recommended daily intake of 25–30 g/day (Kalantar-Zadeh, Kopple, Deepak, Block, & Block, 2002; Krishnamurthy et al., 2012). This suggests that the presence of CKD may have a dramatic impact on the potential beneficial effect of a height fibre diet.

Gum Arabic (GA) is an edible tree gum exudate, which has an important and widespread industrial use as a stabilizer, thickening agent, and emulsifier, mainly in the food industry, but also in the textile, pottery, cosmetic and pharmaceutical industries. Orally ingested GA reaches the large intestine without digestion in the small intestine, it is therefore categorized as a non-digestible carbohydrate or dietary fibre. In traditional medicine, there are anecdotal reports that oral ingestion of GA confirms health benefits, including beneficial effects on kidney function. Two studies undertaken in the Sudan suggest and

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improvement in the biochemical profile of patients with end stage renal failure treated by haemodialysis following dietary supplementation with GA (50 g/day) (Suliman, Hamdouk, & Elfaki, 2000) (A. A. Ali, Ali, Fadlalla, & Khalid, 2008).

Despite hypothetical arguments which support a potential beneficial effect following dietary supplementation of the diet of patients with chronic renal disease, to date no robust clinical studies have been published to determine if such an intervention translates into meaningful clinical benefit. The aim of this clinical trial was to examine the hypothesis that dietary supplementation with GA positively impacts on progression of renal disease in human patients in a clinical setting.

2. Methods

The clinical trial received Ethical approved by The Clinical Trials and Drug Research on Human and Animals Committee of the National Medicines and Poisons Board of the Republic of Sudan and was registered with the Pan African Clinical Trials Registry (ID: PACTR201510001123334). Informed consent was obtained from all subjects.

Patients were eligible for inclusion if aged > 18 years of age with Stage 2 or 3 CKD and progressive renal disease defined as a deterioration in eGFR of ≥ 3 ml/min/year but no>15 ml/min/year and with a minimum of 6 months of follow up results available prior to recruitment. Recruitment was across 7 specialized hospitals in the Sudan. All subjects provided written informed consent. Exclusion criteria were pregnancy, age < 18yrs and any patients with an acute ongoing illness and /or evidence of acute kidney injury.

Enrolled patients had their normal diet supplemented with 25 g of *Acacia senegal* var. *senegal* Gum Arabic daily for twelve months. The daily amount of GA was provided in dried form in individual sealed foil pouches, which was reconstituted in 250 ml of water and shaken to ensure adequate mixing. Compliance was assessed by counting the foil pouches returned to the department. Clinical examination, recording of office seated blood pressure and measurement of biochemical / haematology profiles (serum creatinine, urea and electrolytes, calcium, phosphate, and full blood count) was undertaken monthly. All clinical measurements/investigations were undertaken at a single Joint Commission International (JCI), College of American Pathologist (CAP), United Kingdom Accreditation Service (UKAS) accredited/ certified central laboratory. Haemoglobin was analysed using a Sysmex haematology analyser which uses sodium lauryl sulfate to convert Haemoglobin to a coloured compound that is measured by an automated spectrophotometer. Serum creatinine was measured by Jaffe's Method, Urea was measured by urease and glutamate dehydrogenase methods, Phosphate (Endpoint method) and total calcium (immunoturbidmetric assay) were measured colorimetrically and cholesterol was measured enzymatically, all utilising a COBAS INTEGRA 400 fully automated chemistry analyser. The impact of gum Arabic supplementation on renal function was expressed as reciprocal plot of serum creatinine, mean eGFR within each quarter of the study, and delta eGFR, with eGFR estimates calculated according to the Modification of Diet in Renal Disease Study (MDRD) equation.

At the end of the twelve-month intervention period the GA was stopped, and clinical observations and measurement of biochemical profiles continued for a further 6 months. All patients also received routine/standard clinical care and any additional investigations, which were clinically indicated irrespective of their participation in the study.

Statistical analysis was carried out using SPSS software, version 25 (IBM SPSS, Chicago, I). Student's *t* test was used for analysis of means data, with a P values<0.05 considered statistically significant.

3. Results

A total of 70 patients were recruited. Two patients were withdrawn in the screening period prior to starting GA intervention (dialysis = 1, lost to follow up = 1). Of the 68 patients who started the intervention 41 were male (27 female). The average age of the cohort was 61.5 ± 14.9 years. The primary renal diagnoses of the patients is listed in Table 1. During the 12-month intervention period, 9 patients withdrew from the study (dialysis = 1, died = 3, lost to follow up = 3, transplantation = 2). In addition, a further 15 patients did not complete 6 months of "washout" but did complete 12 months of intervention (dialysis = 6, died = 1, lost to follow up = 8). In total therefore 59 patients completed at least 12 months of intervention with GA and a total of 44 patients completed both the full period of intervention and 6 months of "wash out".

Changes in renal function over the course of the screening, intervention and washout period are shown in Figs. 1-3.

Pre-intervention: Over the six months screening period there was a significant fall in the mean eGFR 28.94 ± 8.99 ml/min to 24.64 ± 8.89 ml/min (p = 0.005). This equated to a mean reduction in eGFR of 8.5 ml/min/year over the pre-intervention period.

Intervention: Following initiation of GA there was an initial statistically significant increase in the mean eGFR at three months (pre 24.64 ± 8.89 vs 26.20 ± 10.1p = 0.02). Subsequently there was no significant fall in the mean eGFR over the period of the intervention (Fig. 1). This translated into a positive mean change in Δ eGFR within quarter at three months, (Δ eGFR 4.89 ml/min/year p=<0.001 vs pre) and six months (Δ eGFR 0.79 ml/min/year, p < 0.001 vs pre) compared to the pre-intervention period (Fig. 2). At 9 months and 12 months although the mean Δ eGFR in quarter was negative representing a decrement, this rate of decline in renal function remained significantly less than the rate prior to the intervention (9 months mean Δ eGFR −1.27 ml/min/year, p= <0.001 vs pre, 12 months mean delta Δ eGFR −1.54 ml/min/year, p < 0.001 vs pre). The linearity observed when the reciprocal of the serum creatinine is plotted against time of follow-up has been used to predict the future course of patients with renal disease. Kidney function (expressed as mean reciprocal creatinine) declined by 11% in the pre-intervention period (Fig. 3). In contrast following initiation of oral supplementation with GA, renal function, expressed as reciprocal creatinine was significantly no different to the pre-intervention values for the duration of the 12 months of the intervention.

Post intervention: Over the six months of the wash out after cessation of Gum Arabic supplementation, mean eGFR did not change, and remained at a level comparable to pre-intervention results (pre 24.64 ± 8.89 ml/l vs post and 6 months 24.29 ± 11.88 and 25.06 ± 11.57 ml/min p > 0.05). At 3 months and 6 months post intervention in the wash out period, although the mean Δ eGFR in quarter was negative representing a decrement, this rate of decline in renal function remained significantly less than the rate prior to the intervention (3 months mean Δ eGFR −1.04 ml/min/year, p= <0.001 vs pre, 6 months mean delta Δ eGFR −0.88 ml/min/year, p < 0.001 vs pre). Similarly, renal function, expressed as reciprocal creatinine was not significantly different after 6 months of the wash out compared to the pre intervention value. For the six patients who completed the intervention, but started dialysis in the post intervention follow up period (male = 5, mean age, 52.67 ± 21.4 years), the mean eGFR prior to intervention was 18.3 ± 4.6 ml/min with

Table 1
Primary Renal Diagnoses.

Primary Renal Diagnosis	Number of patients
Hypertension	23
Diabetes and Hypertension	17
Diabetic Nephropathy	7
CKD cause unknown	8
Polycystic kidney disease	4
Obstructive uropathy	3
Systemic Lupus Erythematosis	1
Drug Induced CKD	1
Tuberculosis	1
No listed diagnosis/missing data	3

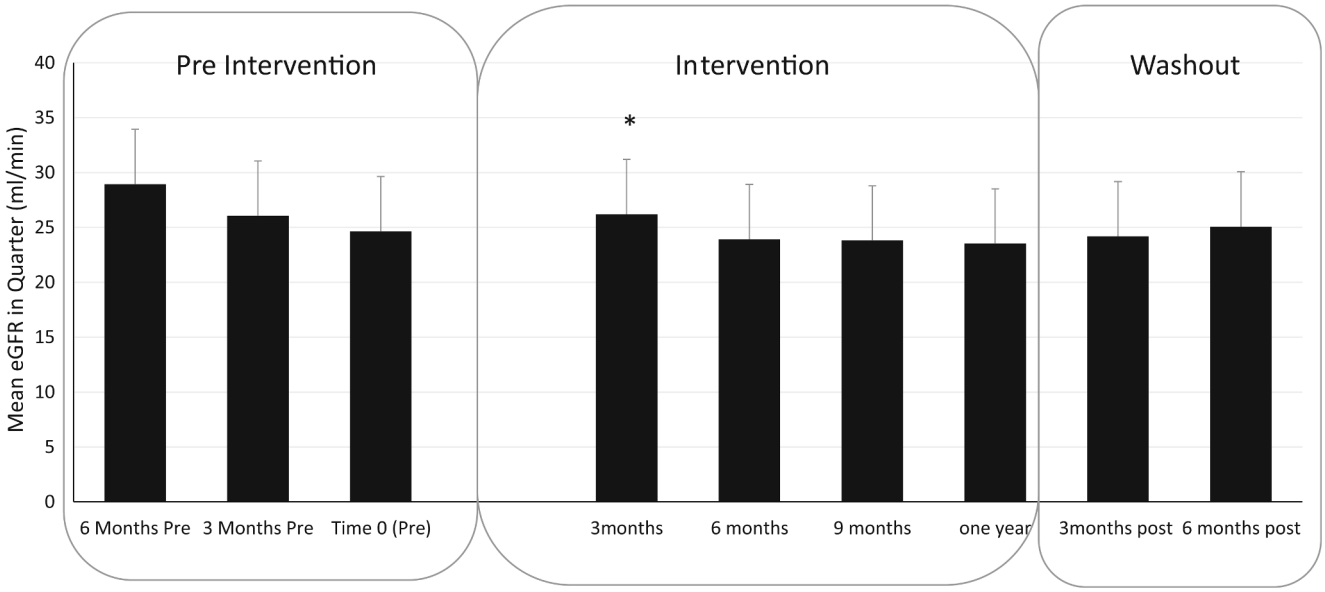

Fig. 1. Effect of Gum Arabic on eGFR. Mean eGFR 6 months, 3 months and immediately prior to dietary supplementation (Pre-intervention), over 12 months of administration of 25 g of Gum Arabic daily (Intervention), and during a 6 months period following cessation of administration of Gum Arabic (Washout). * denotes a statistical increase in eGFR 3 months after initiation of dietary supplementation compared to the eGFR immediately prior to commencing Gum Arabic ($P = 0.02$).

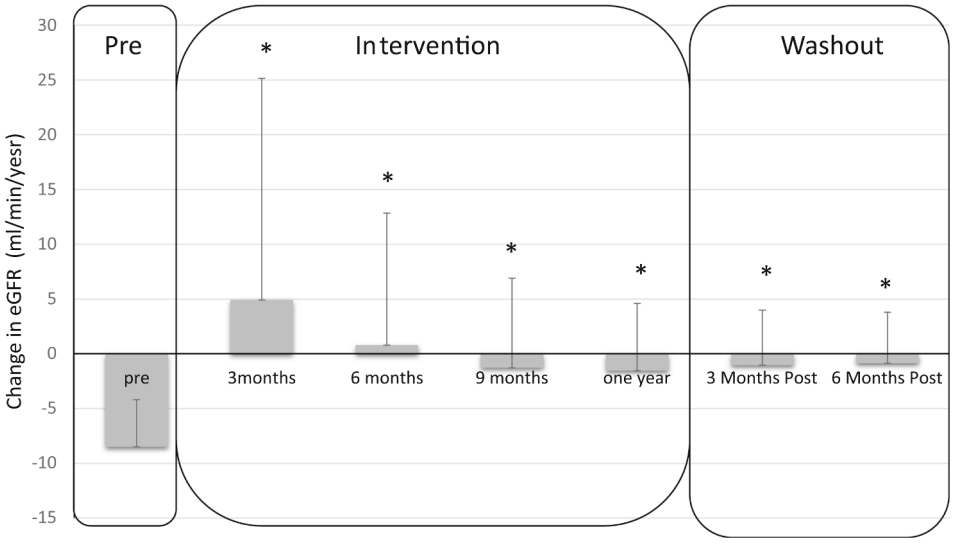

Fig. 2. Effect of Gum Arabic on rate of change of eGFR. Results are expressed as the change in eGFR ml/min/year for each quarter. Pre represents the 3 months prior to initiation, intervention represents changes in each three-month period over the 12 months of administration of 25 g of Gum Arabic daily. Washout represent changes in each quarter over the 6 months following cessation of administration of Gum Arabic. * Denotes $p < 0.001$ comparing the rate of progression to that recorded prior to the intervention (Pre).

a rate of change equating to Δ eGFR 8.76 ± 5.75 ml/min/year. The mean eGFR at the time of starting dialysis was 7.4 ± 5.6 ml/min, and the mean time to starting dialysis from the end of the intervention period was 2.7 months.

Results of other measured parameters are shown in Table 2. In contrast to the changes in serum creatinine (and associated measures of renal function), there were no significant changes in Urea (and electrolytes- data not shown), calcium and phosphate, nor haemoglobin (or other measures of full blood count-data not shown). Results of blood pressure measurements are shown in Fig. 4. There were no significant differences in Systolic Blood pressure (SBP), Diastolic blood pressure (DBP), or Mean arterial pressure (MAP), over the whole course of the study.

4. Discussion

Although there are published data which support potential health benefits of a high fibre diet and more specifically addition of Gum Arabic to the diet, little interventional data have been generated in a clinical context. Intervention studies in animals support a potential beneficial effect of modification of fibre intake (Lee, 1982), and also support a potential role for specifically for Gum Arabic in renal disease, with beneficial effects reported in models of acute kidney injury (B. H. Ali et al., 2010; Mahmoud, Diaai, & Ahmed, 2012). Recent reports suggest GA exerts anti-inflammatory, anti-oxidant and anti-apoptotic roles in mitigating acute renal injury in numerous animal models of acute renal injury (Hammad, Salam, Nemmar, Ali, & Lubbad, 2019; Shafeek, Abu-Elsaad, El-Karef, & Ibrahim, 2019). Data is also emerging that oral administration of GA ameliorates renal injury in models of chronic renal disease by similar anti-inflammatory and anti-oxidant mechanisms (Al Za'abi et al., 2018; B. H. Ali et al., 2015; B. H. Ali et al., 2014; Nasir et al., 2012). Observational data published from the Third National Health and Nutritional Survey (NHANES III) demonstrated a positive association have been described between fibre intake and mortality in human patients with kidney disease (Krishnamurthy et al., 2012). Interventional studies suggesting benefit are however lacking. Evidence that Gum

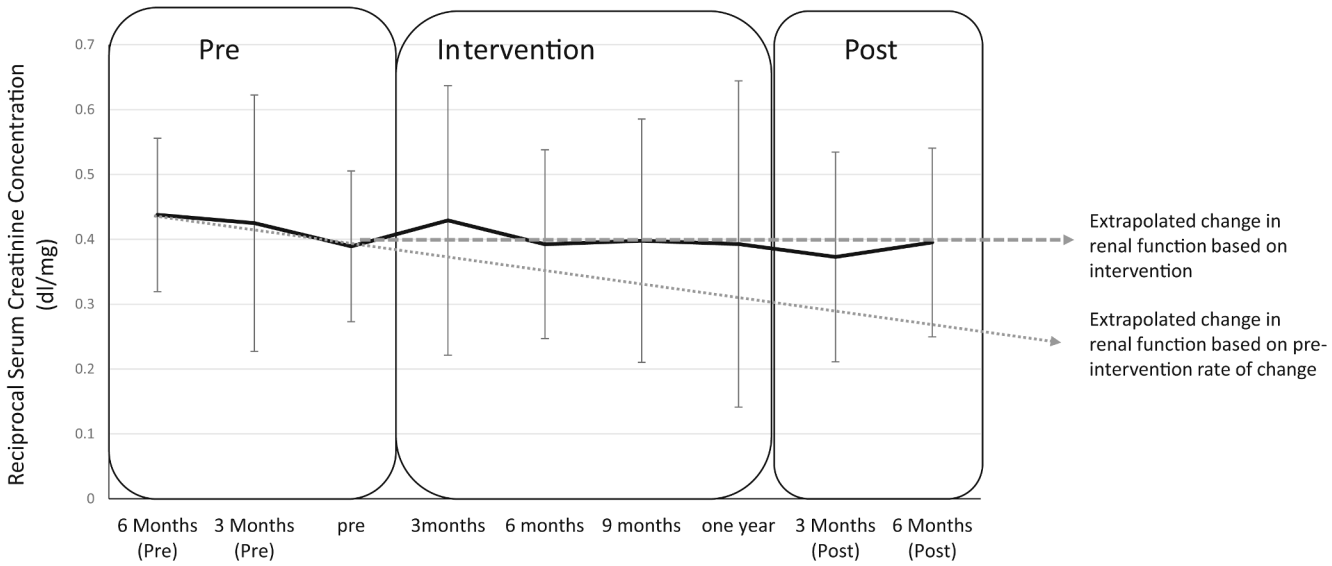

Fig. 3. Effect of Gum Arabic on reciprocal of serum creatinine. Reciprocal of serum creatinine in each quarter in the 6 months screening period (Pre-intervention), over 12 months of administration of 25 g of Gum Arabic daily (Intervention), and during a 6 months period following cessation of administration of Gum Arabic (Washout).

Table2
Biochemical and Haematology results.

	Pre intervention	3 months	6 months	9 months	12 months	3 months post	6 months post
Urea (mg/dl)	87.42 ± 27.46	85.95 ± 36.49	89.93 ± 34.48	86.82 ± 34.94	93.01 ± 46.49	97.22 ± 50.55	88.77 ± 34.37
Hb (g/dl)	12.29 ± 6.54	12.21 ± 4.50	11.63 ± 1.82	11.30 ± 1.92	11.48 ± 2.13	11.53 ± 3.55	11.68 ± 2.24
Cholesterol (mg/dl)	146.68 ± 39.07	150.81 ± 59.40	152.41 ± 58.84	145.71 ± 38.45	145.70 ± 51.59	146.46 ± 50.3	133.77 ± 40.65
Calcium (mg/dl)	8.66 ± 1.31	8.83 ± 1.59	8.53 ± 1.85	8.79 ± 1.19	9.06 ± 1.76	8.70 ± 1.41	8.45 ± 1.91
Phosphate (mg/dl)	4.13 ± 1.94	3.93 ± 0.79	3.87 ± 0.90	3.97 ± 0.90	4.31 ± 1.69	4.19 ± 0.77	3.94 ± 0.89

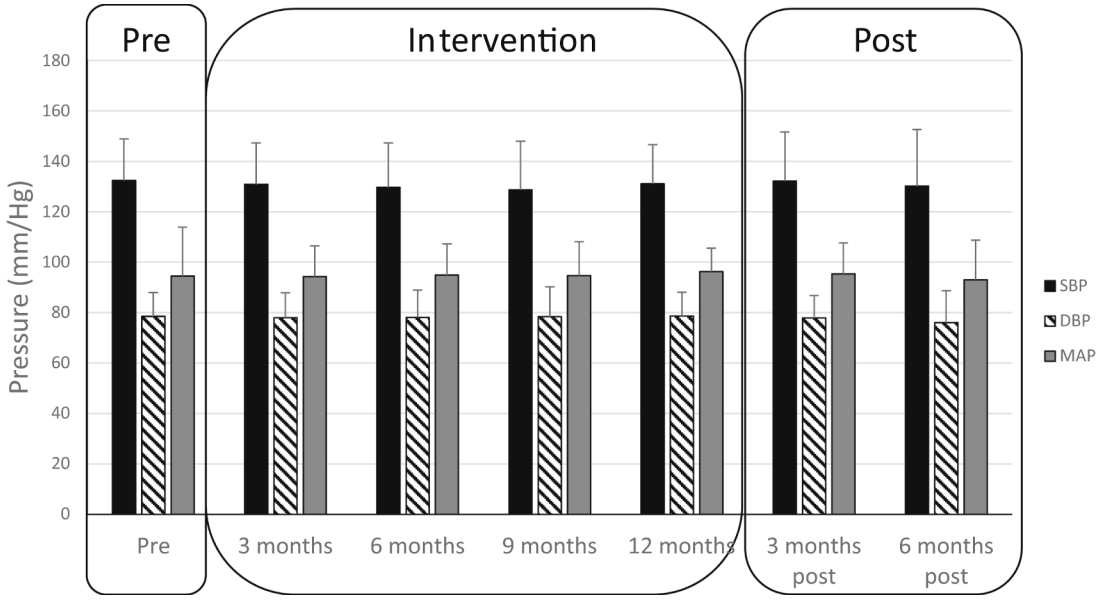

Fig. 4. Effect of Gum Arabic on Blood Pressure. Results are expressed as mean Systolic blood pressure (SBP), mean diastolic blood pressure (DBP) and mean arterial pressure (MAP). There were no significant differences across any of the groups.

Arabic may ameliorate chronic renal disease in human is limited and on the whole anecdotal (Al Mosawi, 2009; Al-Mosawi, 2004; A. A. Ali et al., 2008). Recent studies in both patients with CKD stage 3–4 (Elamin et al., 2017), and haemodialysis patients (N. E. Ali et al., 2020), suggests that daily supplementation with GA reduces measures of oxidative stress and inflammatory markers. How this may transplant to clinical benefit in patients with chronic renal disease prior to the need for dialysis however remains unknown and largely unexplored.

In the present study we provide evidence that oral supplementation with Gum Arabic positively influences the rate of progression of chronic

kidney disease in human patients, and that this effect persists for at least 6 months beyond the period of administration. This therefore supports the hypothesis that manipulation of the dietary fibre content may provide a potential therapeutic avenue in these patients. The data demonstrate a significant reduction in the rate of progression quantified by absolute eGFR, delta GFR and reciprocal of serum creatinine. The linear association of the latter with progression of CKD has been used to predict the likely need for renal replacement therapy. If we assume an eGFR of < 10 ml/min to provide a rough estimation of when patients required dialysis, this translates to a reciprocal creatinine of 0.2 dl/mg. In the patient cohort that we have studied this would (extrapolating from Fig. 3) predict a mean time for starting dialysis for this cohort of 18 months from the start of the intervention period. Assuming this to be a constant rate of progression, we would therefore expect that the majority of the patients included in the trial would have required dialysis over the course of the intervention period and wash-out period. In contrast only one patient was started on dialysis during the 12-month intervention period. An additional 6 patients did start dialysis in the follow-up wash out period. The average time to starting dialysis for the 7 patients who required dialysis was 12.3 months from the start of the intervention. Life expectancy is adversely affected by the need for renal replacement therapy, with a predicated remaining lifetime for patients aged 65yrs (the average age of our cohort) of only 5.4 years (Kramer et al., 2019). Added time free of dialysis in addition to impacting of patient quality of life, therefore also translates to added life expectancy. We have previously demonstrated that oral administration with Gum Arabic in a healthy population did decrease measured systolic blood pressure (Glover, Ushida, Phillips, & Riley, 2009). This study in patients with CKD, however, suggests that the beneficial effect on progression of renal disease is independent on any effect on blood pressure, with no change in SBP, MAP or DBP following initiation of GA or over the 12-month intervention period. It should be noted however that in contrast to many patients with CKD this cohort had well controlled blood pressure prior to the start of the trial (although this was not a prerequisite of recruitment).

A weakness associated with previous dietary fibre studies involving Gum Arabic has been the inherent variable nature of this natural product (Al-Assaf, Phillips, & Williams, 2005). This study of 75 commercial samples showed that their weight average molecular weight varied from 4.6 to 10.2 $\times 10^5$. The traditional Gum Arabic used in the food industry is the exudate from the tree *Acacia senegal* (A. senegal). There are two variety forms available commercially, namely *A. senegal* var. *senegal* and *A. senegal* var. *karensis*. Both are acceptable as food additives and conform to the Specification now approved by the FAO Joint Expert Committee on Food Additives and the Codex Alimenarius Commission. Here we have used an *A. senegal* var. senegal sample which has been matured to give a standardised and reproducible test material, so ensuring that the work can be accurately repeated and that any future product will be able to reproduce the effects reported.

Although beyond the scope of our clinical study, there are published data which may provide mechanistic insight into the basis of our observations. Evidence is emerging that a reduction in ingestion of dietary fibre as is seen in patients with CKD leads to limited substrate fermentation and microbial growth. This leads to a reduction in the amount of amino acids needed for synthesis of microbial protein and an increase in the generation of uremic solutes such as indoxyl sulphate and *p*-cresyl sulphate which may contribute to progression of renal disease. Serum levels of indoxyl sulfate rise in parallel to the loss of kidney function (Wu et al., 2011). Both animal experiments and *in vitro* cell culture work also support a role of indoxyl sulfate in perpetuating a pro-fibrotic response driving a progressive decline in renal function (Miyazaki, Ise, Hirata, et al., 1997; Miyazaki, Ise, Seo, & Niwa, 1997). Similarly evidence is mounting that p-cresyl sulfate serum concentrations are independently associated with overall mortality and are an independent predictor of incident cardiovascular disease in haemodialysis patients (Bammens, Evenepoel, Keuleers, Verbeke, & Vanrenterghem, 2006; Meijers et al., 2008). As a result, reducing the load of colon-derived solutes has been proposed as a potential therapeutic target. One approach is to use sorbents that bind microbial metabolitites such as the carbon-based sorbent AST-120. There are now publications which support this approach (Iida et al., 2006; Nakamura et al., 2011; Owada et al., 2010). An alternative approach would be increase the intake of dietary fibre by oral administration of Gum Arabic as undertaken in this study to, which would be predicted to increasing microbial growth and limit the conversion of amino acids to uremic solutes decreasing the generation of indoles and phenols, which may therefore offer a potential mechanistic basis to our observations. A second mechanism by which oral supplementation with Gum Arabic may provide health benefit is through the increased production of short chain fatty acids, as a product of fibre fermentation. Since SCFA are known to have a host of biologically important effects including modulation of cell proliferation, apoptosis, regulation of angiogenesis and inflammation (Smith, Yokoyama, & German, 1998), as well as reducing the generation and biological activity of pro-fibrotic cytokines (Matsumoto et al., 2006). Consistent with this, we have previously demonstrated in a healthy cohort an increased the concentration of serum butyrate (Matsumoto et al., 2006) and an increase in both serum and faecal total short chain fatty acids concentrations in patients with diabetes and impaired renal function (Glover et al., 2009), following eight weeks of dietary supplementation with Gum Arabic.

In summary our study provides novel evidence that Gum Arabic administered to patients with progressive CKD is well tolerated and is associated with significant beneficial effects, slowing the rate of decline in renal function.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The work described has been carried out in accordance with The code of ethics of the world medical association. The clinical trial received Ethical approved by The Clinical Trials and Drug Research on Human and Animals Committee of the National Medicines and Poisons Board of the Republic of Sudan and was registered with the Pan African Clinical Trials Registry (ID:PACTR201510001123334). Informed consent was obtained from all subjects.

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