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Interaction of Binders in Evaluating the Efficacy of Sevelamer Carbonate Together with Dietary Sources in Hyperphosphatemia Condition

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Abstract:

In the kidneys, nephrons versatility allows for continued normal clearance of plasma solutes. The propensity toward phosphate retention is observed during the cases of chronic kidney disorder (CKD) because of the reduction in the removal of phosphate load. Phosphate-binders administration is still the only true therapy for hyperphosphatemia chronic kidney disorder. Screening of calcium and phosphate levels, during treatment with calcium-containing phosphate binders, is necessary to avoid the possibility of severe hypercalcemia. High serum phosphorus can encourage serum calcium bringing about ectopic calcification. The present study investigates the impact of solutions of plant extracts in combination with sevelamer carbonate on anti-urolithic activity. Kidney stone degradation assay was performed and the weight of the stones was measured consecutively for 72 hours. In the study carried out to find an alternative to reduce the chances of hypercalcemia caused during the treatment of hyperphosphatemia, flax seeds wind up being the best plant source in bringing down the calcium level when administered along with calcium-based phosphate binders and Sevelamer Carbonate. The highest dissolution of stones was found on account of Flax seeds with a percentage dissolution of 5.68%. On the other hand, Chow was found to be the least convincing one as there was an increment in the weight of the stone rather than the stone being disintegrated.

Keywords: Chronic kidney disorder, Phosphate-binders, anti-urolithic, hyperphosphatemia, Sevelamer Carbonate

INTRODUCTION:

Hyperphosphatemia in chronic kidney disorders (CKD) individuals is a likely life-altering state which may result in aerobic calcification, metabolic bone disorders (renal osteodystrophy) as well as the improvement of secondary hyperparathyroidism (SHPT). Hyperphosphatemia is a well-realized risk factor for the aerobic mortality of dialysis patients. Despite technology that is advanced and efficient and regular dialysis therapy the prevalence of hyperphosphatemia remains high [1]. Treatment procedures carried out to treat such kidney conditions are dialysis, a temporary method, or a kidney transplant.

The procedure for the removal of extra water and waste from blood is known as dialysis [2]. It's an artificial replacement of kidney working, particularly in renal failure instances. Sevelamer is utilized to reduced higher blood phosphorus (phosphate) amounts in individuals that are on dialysis as a result of serious kidney disease. Dialysis removes a bit of phosphate from the blood, though it's tough to get rid of enough to keep phosphate levels balanced. Sevelamer works by holding upon phosphate from the diet to ensure that it can pass out of the body.

Sevelamer carbonate, a buffered type of sevelamer hydrochloride, is an orally administered non absorbed phosphate-binding anion exchange resin utilized in the healing of hyperphosphatemia wearing persistent kidney disorders (CKD) [3]. Sevelamer is available in the form of capsules, tablets, etc.

Nature remains as an interminable asset in medical advancement. Since time immemorial, natural products have been the foundation of the customary arrangement of recuperating all through the globe, and have likewise been an integral part of history and culture. Regardless of the present distraction with synthetic science natural products will keep on being critical as sources of medicinal agents. Following the same tradition in the given study we have used extracts of flax seeds, chia seeds, bitter gourd and chow chow to evaluate the efficacy of Sevelamer carbonate under hyperphosphatemia conditions.

Flaxseed (*Linumusitatissimum L.*) is an oilseed used in natural and industrial health solutions [4]. Scientists found that flaxseed incorporated food solutions can have excellent customer acceptability along with their nutritional advantages [5].

Chayote or Chow chow (*Sechiumedule*) is a multipurpose table vegetable generally consumed in Latin American places. Chayote fruits, tuberous roots, and leaves have complex carbs as dietary fiber as well as starch, minerals, and vitamins.

***Momordica charantia L.* (Bitter gourd)** is a flowering vine in the household of Cucurbitaceae. It has an array of the novel as well as biologically active phytochemicals such as steroids, proteins, and triterpenes.

Chia, (*Salvia hispanica L.*), is a dietary and medicinal plant species. Studies suggest that elements of chia seeds have a beneficial impact on the improvement of blood lipid profile, via their immunostimulatory, antimicrobial, hypoglycemic, and hypotensive effects.

The current examination explores the most appropriate plant source among the chosen samples for the treatment of stone formed due to phosphaturia and also for the treatment of hypercalcemia caused due to the use of phosphate binders in cases of hyperphosphatemia.

MATERIALS AND METHODOLOGY:

Plant Source:

Bitter Gourd (*Momordica carantia*) and Chow Chow (*Sechiumedule*): Obtained from Vasanthnagar Market, Bangalore, Karnataka, India.

Flax seeds (*Linumusitatissimum*) and Chia seeds (*Salvia hispanica*): This was obtained from Nature's basket Supermarket, Bangalore, Karnataka, India.

Drug Source:

Sevelamer Carbonate: This drug was obtained from Neetha's Medicals, Bangalore, Karnataka, India.

Types of equipment:

Centrifuge (REMI Laboratory, Maharashtra, India), pH meter (ELICO Ltd. Hyderabad, India/ Model No. LI.120), weighing balance (Shimadzu/ Model No. ELB300), magnetic stirrer (REMI Laboratory, Maharashtra, India), Hot Air Oven.

Chemicals:

Methanol, Sodium Hydroxide, Hydrochloric Acid, Di-Potassium hydrogen ortho-phosphate, Calcium Carbonate, Tris-HCl, Sodium Carbonate, Potassium Permanganate, Magnesium Carbonate, were purchased from Fischer Scientific India Pvt. Ltd., Mumbai, India, Oxalic acid was purchased from HIMEDIA Laboratories Pvt. Lt., Gujarat, India

Preparation of plant extract: The 2 plant samples chow chow (*Sechiumedule*) and bitter gourd (*Momordica carantia*) that were selected were cut and sundried for 2 days. This was finely powdered using a grinder and stored for further usage. 10g of powdered samples in 100mL of methanol were kept on a magnetic stirrer for 30 minutes and centrifuged at 8000 rpm for 15 minutes at room temperature. The pellet was discarded and the supernatant was used freshly with required dilutions.

Preparation of seed extract: The 2 seed samples, Flax seeds (*Linumusitatissimum*) and Chia seeds (*Salvia hispanica*) that were selected were dried in the incubator at 70 degrees Celsius for 24 hours and powdered using a grinder and stored for further usage. 10g of dried samples in 100mL of methanol were kept on a magnetic stirrer for 30 minutes and centrifuged at 8000 rpm for 10 minutes at room temperature. The pellet was discarded and the supernatant was used freshly with required dilutions.

Kidney Stone degradation assay: Surgically removed human kidney stones were procured from M S Ramaiah Memorial Hospital, M S Ramaiah Nagar, Bangalore, Karnataka, India. The assay was performed concerning Rao and Bano method [6], with some minor modifications. The weight of the kidney stones was measured (in grams) and labeled. 40mL of 0.05 M Tris-HCL buffers (pH 5.7) containing 0.15M NaCl was dispensed in various sterile Tarson's containers and labeled accordingly. 2.5mL of 10% methanolic extracts of the sample, 2.5mL of Sevelamer carbonate 2.5mL of standard calcium solution (1mg/mL), and 2.5mL of standard phosphate solution (300ppm) were added in the respectively labeled containers. The evaluated and labeled kidney stones were inoculated in the respective containers. Control was maintained by inoculating the kidney stone in buffer containig10mL of distilled water. The containers were vortexed daily to ensure equal distribution of the sample in the mixture. The weight of the stone was measured after 7 days by drying the stones at 100ºCin a hot air over for 5-7 minutes. % weight reduction was calculated as:

% dissolution = [(Initial weight- Final weight)] /Initial weight × 100.

Estimation of calcium: The amount of calcium present in the samples and the different combinations of sample extracts with the drug was determined using the Titrimetric method.

Standardization of Potassium Permanganate: 10mL of standard oxalic acid was taken in a conical flask along with an equal amount of H_2SO_4. The conical flask was heated to 60ºC and potassium permanganate was added dropwise till the color disappears. The solution was treated against potassium permanganate until concordant values were obtained. The endpoint was the appearance of a permanent pale pink color. The normality of $KMnO_4$ was calculated from the titer value obtained.

Estimation of calcium: To the conical flask containing 5mL of a different combination of solutions 10mL of H_2SO_4 was added and heated till the first bubble appears. The solutions were then treated against standardized potassium permanganate. Duplicates were prepared similarly and titrated for concordant values. From the titer values obtained, the amounts of calcium present in the given samples were calculated.

RESULT AND DISCUSSION:

Chronic kidney disorder (CKD) has become a significant overall healthcare issue. Mineral digestion gives another viewpoint to improving mortality in patients with kidney ailment. Patients with the extreme renal disease suffer from hyperphosphatemia i.e. high serum phosphate levels. Hyperphosphatemia requires severe administration through dietary limitation, dialysis, and utilization of phosphate binders. Sevelamer is used to bring down high blood phosphorus (phosphate) levels in patients who are on dialysis due to extreme kidney disease. Dialysis expels some phosphate from your blood; however, it is hard to remove enough to keep your phosphate levels adjusted. Coronary artery calcification (CAC), a surrogate marker of atherosclerosis, is a typical finding in CKD.

During the time spent attempting to beat such issues dietary sources are currently examined all over the globe for an enormous scope for their noteworthy advantages and their security of no reactions when compared with the engineered drugs.

The effect of the drug (Sevelamer Carbonate) together with the selected plant samples on kidney stones:

Calcium kidney stones are popular worldwide. Most are idiopathic and composed of calcium oxalate. Stone production is multifactorial with a polygenic genetic contribution. Phosphaturia is found frequently among stone formers [7]. Phosphaturia is because of defects in the sodium-phosphate transporter found in the proximal renal tubule. This deformity adds to increased convergence of both calcium and phosphate in the renal loop of Henle and makes conditions that favor stone development. So, variations in the weight of kidney stones were observed when they were placed in the tris-HCL buffer along with the drug and plant sample extract, and the extent of degradation was studied.

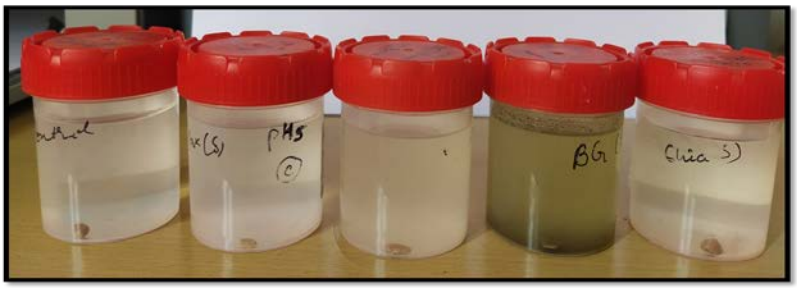

Figure 1: Kidney stones immersed in a tris-HCL buffer along with Sevelamer Carbonate and different plant extracts.

Table 1: Difference in the weight of the stones when observed every day for 72 hours immersed in a tris-HCL buffer along with Sevelamer Carbonate and different plant extracts.

Time (hours)	Control (grams)	Flax seeds (grams)	Chia seeds (grams)	Bitter gourd (grams)	Chow chow (grams)
0	0.0592	0.0334	0.0940	0.0506	0.0472
24	0.0592	0.0323	0.0943	0.0509	0.0477
48	0.0592	0.0320	0.0946	0.0515	0.0447
72	0.0592	0.0315	0.0950	0.0521	0.0509

Table 2: Amount of Calcium present in the dietary sources when combined with calcium-based phosphate binder (Sevelamer Carbonate) and non-calcium-based phosphate binders (Calcium carbonate and magnesium carbonate)

Dietary Sources	Sevelamer Carbonate (mg)	Calcium Carbonate (mg)	Magnesium Carbonate (mg)
Flaxseeds	0.364	1.092	0.728
Chia Seeds	0.364	0.546	0.546
Bitter Gourd	1.638	1.82	1.456
Chow Chow	2.184	2.73	2.184

Kidney stones are mineral deposits in the renal calyces and pelvis that are present free or joined to the renal papillae. As urine becomes supersaturated with mineral crystalline organic components consisting of stones are formed. Calcium oxalate is the principal constituent of most stones. Obesity, diabetes, hypertension, and metabolic disorder are viewed as hazard factors for stone formation, which, thus, can prompt hypertension, chronic kidney disease, and end-stage renal ailment [8]. Hypercalciuria frequently advances kidney stone formation. Calcitriol, the active metabolites of Vitamin D increase digestive calcium absorption and could hypothetically increase calciuria prompting kidney stone formation [9]. The best example which demonstrated the most elevated disintegration of the kidney stones alongside Sevelamer Carbonate was flax seeds with a dissolution percentage of 5.68%. The highest percentage dissolution of kidney stones was seen in a solution containing flax seed extract amongst all the samples Bitter Gourd, Chia seeds, Chow Chow indicated negative outcomes as there was an increase in the weight of the kidney stone.

Effect of the drug with different plant sources on the calcium level:

At the point when the measure of calcium present in chosen samples alongside various sorts of phosphate binders was determined through the titrimetric technique, flaxseeds wind up being the best plant source in bringing down of the calcium level when it was directed close by the non-calcium-based phosphate binder Sevelamer Carbonate followed by magnesium carbonate and afterward calcium carbonate. Chow chow was seen as the least convincing one.

The measure of phosphate in the blood influences the degree of calcium in the blood. Calcium and phosphate in the body respond in inverse ways: as blood calcium levels rise, phosphate levels fall. A hormone called parathyroid hormone (PTH) controls the degrees of calcium and phosphorus in our blood. Hyperphosphatemia builds serum calcium, prompting lower-than-ordinary degrees of ionized calcium. The reduction in ionized calcium triggers the release of PTH, bringing about a condition of secondary hyperparathyroidism. Hyperphosphatemia is a significant reason for morbidity and mortality in patients with CKD. The relationship among hyperphosphatemia and expanded danger of death from cardiovascular infection/vascular calcification have been established for quite a while [10].

Patients with end-stage renal disease (ESRD) hold phosphorus and develop hyperphosphatemia. High serum phosphorus can encourage serum calcium bringing about ectopic calcification. Hyperphosphatemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency. An expansion in parathyroid hormone (PTH) levels is normal for patients with chronic renal failure. Expanded degrees of PTH can prompt osteitis fibrosa, a bone sickness. A lessening in serum phosphorus may diminish serum PTH levels. Treatment of

hyperphosphatemia includes a decrease in dietary admission of phosphate, restraint of intestinal phosphate assimilation with phosphate binders, and removal of phosphate with dialysis [11].

Cardiovascular calcification prompts bleakness and mortality. Patients experiencing constant kidney infection have been believed to display expanded quickened calcification of the intima, media, heart valves just as myocardium, and an uncommon condition called uraemic arteriolopathy (calciphylaxis). An unevenness of the promoters, for example, calcium and phosphates are focal in the improvement of calcification [12].

Phosphate covers are generally used to bring down serum phosphorus levels in individuals with chronic kidney disease (CKD) yet their effect in CKD stays questionable. Accessible phosphate binding agents have been found to diminish phosphorus levels in contrast with placebo. Be that as it may, there are lacking information to build up the near predominance of novel non-calcium binding agents over calcium-containing phosphate binders for example, all-cause mortality and cardiovascular end-focuses in CKD [13].

Among bitter gourd, chow chow, chia seeds, and flax seeds, chow chow end up being the most potential one in lessening phosphate level and keeping up appropriate calcium balance in the body when brought with the medication, Sevelamer carbonate. Diet assumes a significant job alongside prescription in bringing back legitimate ion concentration in the body. Chow chow may be recommended close by the prescribed medication for a quick and superior outcome. Another weapon has been found in phosphate control.

Just 50% of the patients being treated with phosphate binders supposedly achieved the suggested serum phosphate levels. Hemodialysis patients were accounted for to show a straight connection of hyperphosphoric salivary content with serum phosphate, it was guessed that coupling salivary phosphate during times of fasting notwithstanding utilizing phosphate binders with suppers could improve the treatment of hyperphosphatemia. The expansion of salivary phosphate binding to conventional phosphate binders could be a valuable methodology for improving the treatment of hyperphosphatemia in HD patients [14].

CONCLUSION:

The present study explored different plant samples, for example, flax seeds, chia seeds, bitter gourd, and chow. As of late, admission of flax seeds and chia seeds has become a pattern because of its numerous nutritious focal points. Calcium stones are the most widely recognized kind of kidney stones and can be either calcium oxalate or calcium phosphate. Calcium phosphate stones are less normal than calcium oxalate stones. They are brought about by an excessive amount of calcium in urine, a lot of phosphate in the urine, or too little citrate in the urine. In the given study kidney stone degradation assay was performed to check which of the selected samples was effective in reducing the size of the kidney stone and thus can be incorporated in the diet. Usually hydration is the key measure in the removal of kidney stones and rarely any medications are required. But sometimes the conditions worsen and solubilizing the stone isn't an option. In such cases one can rely on the consumption of flax seeds rather than bombing the body with synthetic drugs. Hyperphosphatemia is an abnormally elevated level of serum phosphate that adds to chronic kidney disease (CKD). The administration of hyperphosphatemia has included dietary phosphate limitation and the utilization of phosphate fasteners. So, the amount of calcium present in the selected plant extracts was estimated along with calcium-based phosphate binders and alone. This estimation showed that flax seeds can be consumed when patients are under medication for hyperphosphatemia so that the chances of being affected by hypercalcemia becomes minimal or nil.

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