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Research article

KID-T, a unique polyherbal extract, improves feline patients with azotemia and uremia: A pilot study

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Abstract

The use of integrative and alternative therapies, including herbal medicines, is becoming increasingly common for the treatment of cats with azotemia and uremia. KID-T was initially developed as a therapeutic agent to improve renal function in humans. The objective of this study is to assess the effectiveness of KID-T, a natural supplement comprised of 18 distinct herbs, in ameliorating renal dysfunction in feline patients afflicted with azotemia and uremia. A total of four cats were enrolled in the study and were administered KID-T orally twice daily for three months. Blood biochemical profiles were monitored each month to assess the safety and efficacy of KID-T. The results indicated that KID-T was well-tolerated and relatively safe during the treatment period. Furthermore, after three months of treatment, the levels of ammonia, blood urea nitrogen, and creatinine in all cats were relatively close to the normal reference range, and the urine protein-creatinine ratio decreased. Additionally, clinical examination and biochemical profile revealed that renal function was stabilized for the entire duration of the study. Overall, this study suggests that KID-T may improve and maintain renal function in feline patients with azotemia and uremia. Future research should explore other potential benefits of KID-T in feline renal patients, such as assessing the quality of life and patient-owner satisfaction.

Keywords: Feline azotemia, KID-T, Uremia.

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INTRODUCTION

Natural botanical compounds have been used for centuries in the management of various diseases, including kidney diseases. Some botanical extracts can aid in the excretion of toxins in the kidneys, thereby improving azotemia and uremia symptoms (Donato, 2010; Huang et al,. 2018). The PET-XELL BIO Co., Ltd, a company based in Seoul, Korea, has developed a novel product named KID-T, whose composition is detailed in Table 1. The product is based on a modification of Nephricare®, a human product whose information can be found at https://fda.report/DailyMed/cfeb9cad-9266-9d17-e053-2a95a90a5532. The KID-T contains 18 different plant extracts and the main ingredients are *Rehmannia glutinosa*, *Dioscorea batatas*, and *Cornus officinalis*, which have traditionally been used in human medicine to treat chronic aplastic anemia and primary chronic glomerulonephritis (Yuan et al., 1998; Qiu et al., 2014) .

Renal failure and kidney disease are common in cats and are the leading causes of death (Polzin, 2011; Bartges, 2012; Polzin, 2013; White et al., 2013; Matchimakul, 2018). Chronic kidney disease (CKD) is a common condition in cats, with estimates suggesting that up to 30-40% of cats over the age of 10 may be affected (Lulich, 1992; Sparkes et al., 2016). Feeding a kidney-specific diet that is restricted in phosphorus and protein content, while providing adequate levels of essential amino acids, vitamins, and minerals, has been shown to slow the progression of CKD and improve quality of life in affected cats (Roudebush et al., 2009; Korman et al., 2013). Other interventions, such as management of hypertension, control of proteinuria, and the use of antioxidant supplements, may also be beneficial in some cases (Roudebush et al., 2009). However, the success of these treatments can depend on the severity and stage of the disease, as well as individual patient factors. As natural herbal medicines can provide a comprehensive therapeutic approach that takes into account the overall condition of the patient and can be used as a single or adjunctive treatment for patients with kidney disease (Wynn et al., 2003), the present study of KID-T could be used in this context, and further research is warranted.

In this study, we investigate the toxicity of KID-T in feline cell lines, as well as to evaluate its effectiveness and tolerability in improving renal function in cats. Given their potential to treat chronic kidney diseases and prevent recurrence, herbal remedies like KID-T could offer veterinarians a viable and safe treatment option.

MATERIALS AND METHODS

KID-T

KID-T was provided from PET-XELL BIO Co., Ltd (Seoul, Korea). KID-T is a powdered blend derived from 18 natural herbs. The herbal ingredients of KID-T are shown in Table 1. KID-T was administered as a capsule to the patients and was dissolved in dimethyl sulfoxide (DMSO) for *in vitro* experiments.

In vitro: Cell viability assay

The feline kidney cell line, Crandell-Rees Feline Kidney (CRFK) was purchased from the Korean Cell Line Bank (Seoul, Korea) and Canine progenitor epidermal keratinocytes (CPEK) were purchased from CELLnTEC (Bern, Switzerland). Both cells were grown in Dulbecco's Modified Eagle Medium containing 10% fetal bovine serum. The CPEK and CRFK cells were dispensed into a 96-well plate and cultured in a humidified CO2 incubator (37°C, 5% CO2) for 1 day and treated with KID-T at various concentrations (0, 1, 10, 50, and 100 μg/ml) dissolved in DMSO for 24 h (n = 3). Cell viability was measured using CellTiter 96 AQueous One solution kit (Promega, Madison, WI, USA) and a microplate reader (Multiskan™ FC Microplate Photometer, Thermo Scientific, Waltham, MA, USA).

Table 1 Composition and doses of herbal extracts in KID-T used *in vitro* and *in vivo*

Compounds	Percentage (%)	Dose (mg) in 400 mg KID-T capsule
Rehmannia glutinosa Liboschtz var.purpurea Makino	22%	88
Dioscorea batatas Decaisne	13%	52
Cornus officinalis Siebold et Zucc	13%	52
Poria cocos Wolf.	11%	44
Cuscuta japonica Choisy	6%	24
Cinnamomum cassia Blume	3%	12
Asparagus lucidus Lindley	3%	12
Ophiopogon japonicus Ker-gawler	3%	12
Cistanche deserticola Y. C.	3%	12
Achyranthes japonica NaKai	3%	12
Eucommia ulmoides Oliver	3%	12
Lycium chinense Miller	3%	12
Schizandra Chinensis Billon	3%	12
Panax Ginseng C.A. Meyer	3%	12
Rubus crataegifolius Bunge	2%	8
Plantago asiatica L.	2%	8
Acorus gramineus Solander	2%	8
Polygala tenuifolia L.	2%	8
Total	**100%**	**400**

In vivo: Clinical pilot study

Four cats diagnosed with kidney disease at Dr. Oh's Hwanggum Animal Medical Center (Daegu, South Korea) were enrolled in this study. Patient information is summarized in Table 2 and 3. The mean age of the patients was 7.0 years, and the mean weight was 5.28 kg. A clinical trial of KID-T was conducted after administering 1 capsule per 5 kg of KID-T twice a day for 3 months. The patient's weight, body temperature, blood pressure, and clinical symptoms were checked, and blood tests (i.e., complete blood count and biochemical profiles) and urine inspection were performed.

Table 2 Information of patient cats supplemented with KID-T for 3 months

Case #	Breed	Body weight (kg)	Age (yrs)	Sex	Diagnoses
1	Korean shorthair	6.3	10	MC	Chronic kidney disease, Uremia, Pyelonephritis, Cystitis, Hypertrophic cardiomyopathy, Anemia, Microhepatica
2	Korean shorthair	5.2	3	MC	Renal failure, Uremia, Pyelonephritis, Cystitis, Hypertrophic cardiomyopathy, Microhepatica, Chronic constipation, Megacolon
3	Turkish Angora	6.2	8	MC	Chronic kidney disease, Uremia, Pyelonephritis, Cystitis, Hypertrophic cardiomyopathy, Microhepatica
4	Siamese	3.4	7	FS	Chronic kidney disease, Uremia, Pyelonephritis, Cystitis, Hypertrophic cardiomyopathy, Microhepatica, Chronic constipation

Table 3 Physical examination and clinical symptom evaluation of 4 cats participating in the KID-T administration clinical trial

Case #	Examination		Reference	Unit	0 m	1 m	2 m	3 m
1	Physical exam	Body weight		kg	6.3	6.3	6.2	6.1
		Body temp.	38~39.3	°C	39.4	38.8	38.3	38
		Blood pressure	100-140	mmHg	120	120	120	110
	Clinical signs	Appetite	Good/Fair/Poor		Poor	Fair	Fair	Fair
		Vomiting	Yes/No		Yes	No	No	Yes
		Feces	Normal/Abnormal		Abnormal	Normal	Normal	Abnormal
		Urine	Normal/Abnormal		Abnormal	Abnormal	Abnormal	Abnormal
2	Physical exam	Body weight		kg	5.2	5.3	5.2	5.1
		Body temp.	38~39.3	°C	38.9	38.5	39.1	38.7
		Blood pressure	100-140	mmHg	140	130	130	120
	Clinical signs	Appetite	Good/Fair/Poor		Poor	Fair	Fair	Fair
		Vomiting	Yes/No		Yes	No	No	No
		Feces	Normal/Abnormal		Abnormal	Normal	Normal	Abnormal
		Urine	Normal/Abnormal		Abnormal	Normal	Normal	Normal
3	Physical exam	Body weight		kg	6.2	6.3	6.2	6.2
		Body temp.	38~39.3	°C	39.2	38.7	38.3	38.9
		Blood pressure	100-140	mmHg	110	120	110	120
	Clinical signs	Appetite	Good/Fair/Poor		Poor	Fair	Fair	Fair
		Vomiting	Yes/No		Yes	No	No	No
		Feces	Normal/Abnormal		Abnormal	Normal	Normal	Abnormal
		Urine	Normal/Abnormal		Abnormal	Normal	Normal	Normal
4	Physical exam	Body weight		kg	3.4	3.5	3.3	3.3
		Body temp.	38~39.3	°C	38.9	39.1	39.2	38.2
		Blood pressure	100-140	mmHg	120	130	120	120
	Clinical signs	Appetite	Good/Fair/Poor		Poor	Fair	Fair	Fair
		Vomiting	Yes/No		Yes	No	No	No
		Feces	Normal/Abnormal		Abnormal	Abnormal	Abnormal	Normal
		Urine	Normal/Abnormal		Abnormal	Normal	Normal	Normal

Statistical analysis

The results are presented as mean ± standard deviation. One-way analysis of variance (ANOVA) was carried out to analyze the result of cell viability assay. Differences between pairs of means were compared using a Bonferroni test. P-values of less than 0.05 were used to denote statistical significance.

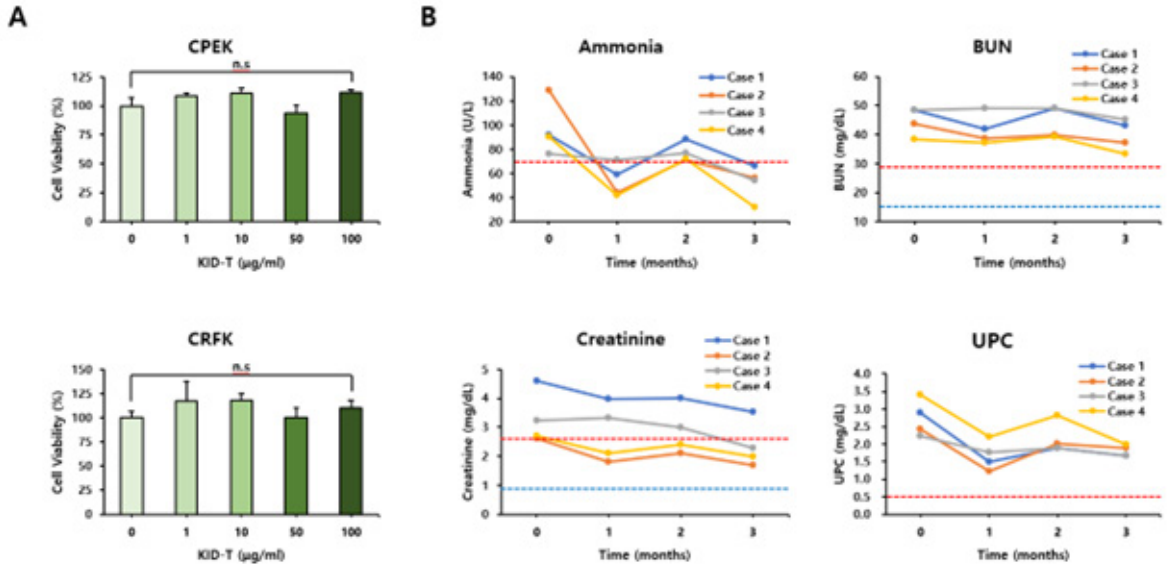

Figure 1A CPEK and CRFK were grown and treated with the indicated doses of KID-T (i.e., 1, 10, 50, and 100 μg/mL) for 24 h (n=3). The control was 0.1% DMSO. The CellTiter 96 AQueous One solution was used to measure cell proliferation. Data are presented as the mean ± standard deviation of three replicates. B) KID-T affects several serum chemistry parameters in cats supplemented with KID-T for 3 months. Serum chemistry data of the blood samples collected from cats supplemented with KID-T for 3 months; ammonia, blood urea nitrogen, creatinine, urine protein–creatinine ratio. } The normal range is represented by the red and blue lines.

RESULTS

In vitro: Cell viability assay

Cell experiments of KID-T were conducted to determine whether toxicity was observed at the cellular level. CPEKs and CRFKs were used to evaluate the toxicity of KID-T. CPEKs and CRFKs were treated with KID-T for each concentration for up to 24 h. As a result, no significant toxicity was observed after administration of up to 100 μg/mL of KID-T until 24 h (Figure 1a).

In vivo: Clinical pilot study

The blood tests revealed that before KID-T administration, ammonia level was higher than the normal range in all cases and decreased to the normal range 1 month after KID-T administration and showed a general decrease over 3 months (Figure 1b). The blood urea nitrogen value for measuring blood nitrogen concentration showed a slow decrease in cases 1, 2, and 4 but did not decrease to the normal range even after 3 months of KID-T administration. The serum creatinine level was higher than the normal range before administration; however, during KID-T administration for 3 months, the serum creatinine level in all cases gradually decreased. Particularly, cases 2 and 4 showed a decrease to the normal range 1 month after KID-T administration, and case 3 showed a decrease to the normal range after 3 months. The urine protein–creatinine ratio was higher than the normal range in all cases before KID-T administration and tended to decrease slightly over 3 months but did not decrease to the normal range in all cases.

DISCUSSION

Kidney disease in cats is the most common disease in small animal clinical practice worldwide (Polzin, 2011; Bartges, 2012; Polzin, 2013; White et al., 2013). Patients often die within a few years while receiving treatments, such as fluid therapy and hemodialysis. Therefore, a new and effective therapeutic approach for kidney disease in cats accompanied by severe azotemia and uremia is required. Among new approaches, herbal remedies for patients with kidney diseases have recently attracted global attention because of their low toxicity and relatively easy availability (Wynn et al., 2003; Wynn et al., 2007). In an effort to enhance the biological activity of a singular compound, a composite herbal formulation, KID-T, was synthesized using 18 herbs exclusively utilized for treating kidney disease. The KID-T is based on a modification of Nephricare®, a human product whose information can be found at https://fda.report/DailyMed/cfeb9cad-9266-9d17-e053-2a95a90a5532. Despite the complexity of the kidney's cellular composition, intricate structure, and constrained regenerative capacity, demonstrating the therapeutic potential of a drug on the kidney via a single cell line experiment poses difficulties. Nevertheless, our findings revealed that KID-T exhibited no observable cell toxicity up to a concentration of 100 μg/ml (Figure 1a), implying that KID-T may not prompt cell death in both feline and canine cells.

This study was a pilot study that has evaluated the safety and efficacy of renal therapy in cats with kidney disease using KID-T. Blood ammonia is converted to urea in the liver via the urea cycle, which is eventually evaluated in the blood as blood urea nitrogen. Therefore, decreasing the ammonia concentration in the blood is essential to lower blood urea nitrogen levels in patients with kidney disease (Narasimhan et al., 2001; Imran et al., 2012; Adagra et al., 2015; Carvalho et al., 2021). Azotemia and uremia in patients with hyperammonemia are factors that aggravate kidney disease (Imran et al., 2012; Adagra et al., 2015; Carvalho et al., 2021). After administration of KID-T, ammonia levels, which were higher than the normal range before administration, decreased, suggesting that KID-T improves hyperammonemia and particularly contributes to liver detoxification and kidney toxin excretion functions. Particularly, in the case of kidney disease, the nitrogen concentration in the blood increases, resulting in azotemia and uremia symptoms (Elliott, 2006; Polzin, 2011; Polzin, 2013; White et al., 2013). After administration of KID-T, blood urea nitrogen levels, which were higher than the normal range before administration, decreased. Blood creatinine is also used as an index to evaluate renal function (Polzin, 2011; Polzin, 2013; White et al., 2013), and we found in this study that it gradually decreased to the normal range, suggesting that KID-T improves the creatinine excretion rate. This may be related to improved renal function with decreased creatinine levels after treatment. Kidney disease improvement was confirmed using a urine protein–creatinine ratio test, and a gradual decrease was shown in all cases, suggesting that KID-T contributes to kidney protection by delaying the progression of kidney damage. In this study, renal function improved with auxiliary indicators, such as blood urea nitrogen, creatinine, and the urine protein–creatinine ratio. Thus, the safety and efficacy of KID-T can be provided as evidence that this preparation can be

applied to feline patients with kidney disease. Based on the clinical profiles, KID-T has been tried as a pilot study as a treatment and palliative therapy for feline kidney disease and that it is possible that such a treatment could be tried in cats in the future, as in humans.

For successful management of feline chronic kidney disease, systematic therapeutic management includes 1) dehydration and electrolyte correction with fluids, 2) slowing the progression of kidney damage with a low sodium/low phosphorus/low protein diet, 3) improve high blood pressure with blood pressure medication, 4) correct hyperparathyroidism if present, and 5) pharmacotherapy to improve clinical signs (vomiting, diarrhea, anorexia) due to uremia: antiemetics, antidiarrheals, antacids, and appetite stimulants may be needed. Since these conventional treatments has not been successful in many cases, new treatment or management is required.

However, this study has some limitations. First, this study had a small sample size. In this study, KID-T was administered to only four cats with kidney disease; however, this number was insufficient for a complete evaluation of the therapeutic efficacy and safety of KID-T. Second, in this study, compared with the maximum recommended dose for humans, we found that the dose concentration of 80 mg/kg/day twice daily might be better for feline patients with kidney disease. However, appropriate concentrations for various kidney diseases in cats should be optimized in further clinical trials involving feline patients with kidney diseases. Therefore, long-term administration of KID-T in feline patients with kidney disease and long-term observation in a large clinical cohort are thought to provide more information on the clinical efficacy and safety of KID-T.

CONCLUSIONS

Based on the results of a preclinical study involving four cats with kidney disease, KID-T has demonstrated effectiveness as a treatment and palliative therapy. The administration of KID-T was observed to be safe and effective in all cats with kidney disease, as assessed by a blood biochemical profile analysis. Although only a blood biochemical profile was utilized to evaluate the clinical response, it was confirmed that KID-T can be safely administered without significant adverse effects. Further research in large-scale clinical trials is required to determine the efficacy of KID-T in treating feline patients with kidney disease.

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AUTHOR CONTRIBUTIONS

All authors have made considerable contributions to this work. Conceptualization: WO, MK, and SJB; Methodology: WO and IK; Analysis and investigation: WO, IK, MK, and SJB; Writing–original draft preparation: WO and SJB; Writing – review and editing: WO, IK, MK, and SJB.

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