◆ Original research ◆

Evaluation of the Kidney Function –Improving Effects of *Angelica shikokiana* Using Animal Models

Motohiro Hayashi [1], Eiji Mitate [2*]

*Corresponding author: Eiji Mitate [2]

Affiliated institutions:

[1] Hayashi Technical Laboratory Co. [2-3-21-606, Kabuki-cho, Shinjuku-ku, Tokyo 160-0021, Japan]

[2] Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Kanazawa Medical University. [1-1 Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920-0293, Japan]

Abstract

Angelica shikokiana is an endemic Japanese plant belonging to the *Apiaceae* family. Its roots are rich in coumarin derivatives, including isopteryxin and isoepoxypteryxin (YN-1), as well as various vitamins, minerals, and amino acids. Previous studies reported multiple biological activities, such as the suppression of blood glucose elevation, inhibition of platelet aggregation, neuroprotection, vasodilation, and antihypertensive effects. Herein, we focused on the effects of *Angelica shikokiana* on renal function in dogs and cats by retrospectively and prospectively analyzing blood test data obtained during routine veterinary practice.

In Study 1, changes in blood urea nitrogen (BUN) and serum creatinine (Cr) levels were analyzed in 56 cats and 38 dogs. A high proportion of values fell below the baseline, suggesting renal function–improving effects. In Study 2, the data at baseline and 30, 90, and 240 days were evaluated for 142 cats and 55 dogs. Significant reductions in BUN and Cr levels were observed in cats with stage 1 and 2 renal impairment, whereas no statistical significance was detected in dogs. Nevertheless, long-term administration in dogs tends to stabilize or improve renal function.

Our findings suggest that continuous administration of *Angelica shikokiana* may be effective in improving or maintaining renal function, particularly in cats with early to-moderate renal impairment. Daily supplementation appears to be useful for renal support and evaluation over a minimum of 90 days is recommended.

Key Words：Angelica shikokiana, Isoepoxypteryxin, Isopteryxin, YN-1, Kidney Disease, Renal function

1. Introduction

Angelica shikokiana is a perennial plant belonging to the genus Angelica of the family *Apiaceae*. It is endemic to Japan and is distributed across the Kii Peninsula, Shikoku, and Kyushu. They grow on mountain slopes, rocky cliffs, riverbanks, and streamside rocky areas [1)].

The roots of *Angelica shikokiana* contain coumarin compounds, such as isopteryxin and isoepoxypteryxin (YN-1), as well as many vitamins, minerals, and amino acids [2)]. Its effects are diverse and include the suppression of blood glucose elevation [3)], inhibition of platelet aggregation [4)], neuroprotective effects [5)], vasodilatory activity [6)], and antihypertensive effects [7)]. Currently, many commercial health foods and supplements are available in Japan. Among them, in dogs and cats administered with *Angelica shikokiana* as a dietary supplement, improvements in blood urea nitrogen (BUN) and serum creatinine (Cr) were observed.

Therefore, here, we retrospectively analyzed blood test results from routine clinical practice, focusing on renal function, and examined the usefulness of *Angelica shikokiana*.

2. Materials and Methods

Cases in which an *Angelica shikokiana* product (JIN Power 100, Hayashi Giken Co., Ltd., Tokyo) was

administered at ~0.1 g per 3 kg body weight per day, mixed into pet food or treats, were included. Blood test results were obtained from routine health checks or clinical visits to primary veterinary hospitals. BUN and Cr values were expressed as ratios relative to the pre-administration values (set as 1).

2.1. Study 1

To understand the trend of renal function changes with *Angelica shikokiana*, data were retrospectively collected from 56 cats (9.8 ± 3.3 years) and 38 dogs (10.1 ± 3.2 years) for BUN and Cr.

2.2. Study 2

Prospective data were collected from 55 dogs (10.1 ± 3.2 years) and 142 cats (10.2 ± 3.1 years) at pre-administration, and at 30, 90, and 240 days after administration. As in Study 1, BUN and Cr values were expressed as ratios relative to those of the pre-administration values (set to 1). Pre-administration renal impairment was staged by attending veterinarians using the International Renal Interest Society (IRIS) staging system (2023 version)[8].

2.3. Statistical Analysis

For comparisons among stage groups in Study 2, the Kruskal-Wallis test was used, with $p < 0.05$ being considered as statistically significant. All statistical analyses were performed using EZR (Jichi Medical University, Tochigi, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria)[9].

3. Results

3.1. Study 1

The total number of measurements was 56 and 38 for cats and dogs, respectively (**Fig. 1**). Among them, values less than or equal to 1 relative to those of the pre-administration were observed in 48 cat BUN (87%), 46 cat Cr (84%), 30 dog BUN (79%), and 30 dog Cr (79%) measurements (**Fig. 1**).

The maximum and minimum BUN values in the cats

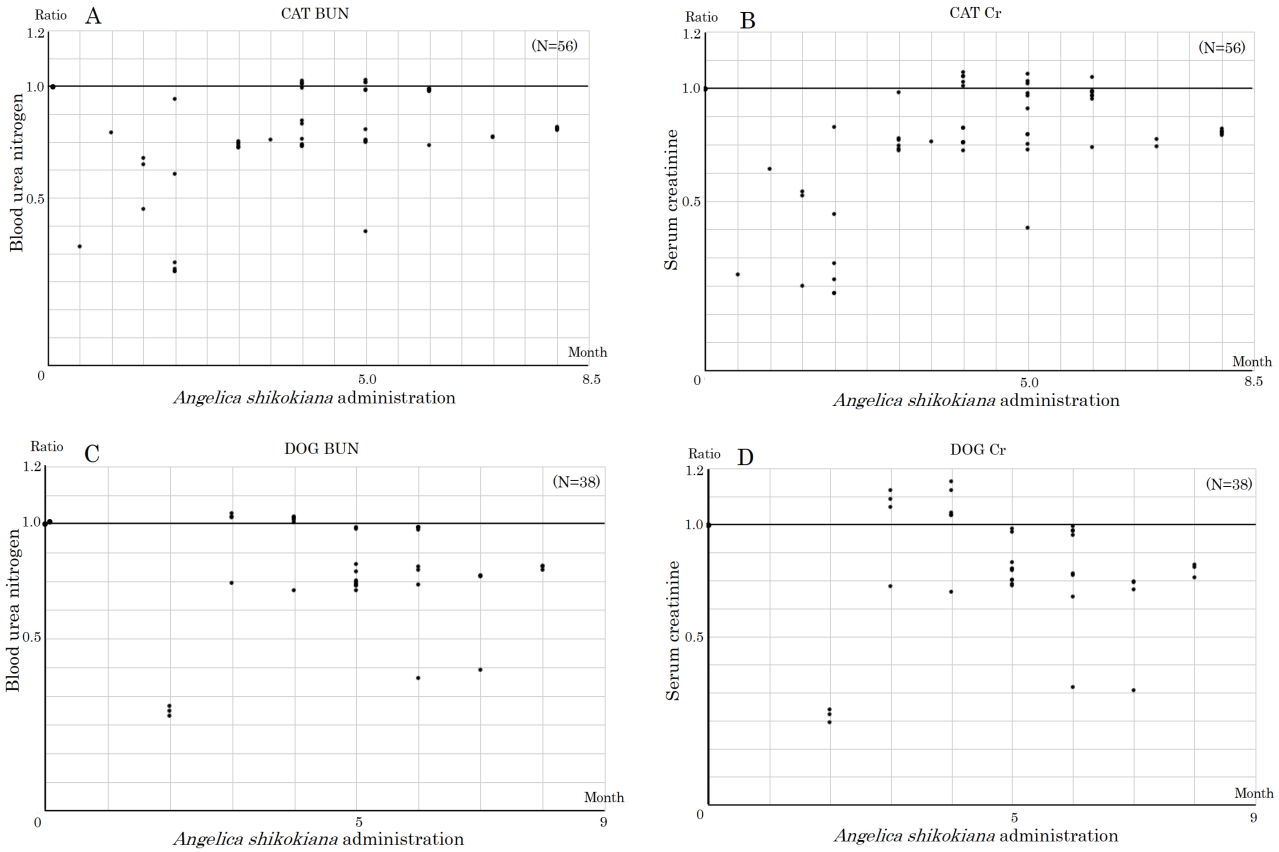

Fig. 1. Blood test results

Changes in blood urea nitrogen (BUN) and serum creatinine (Cr) in cats (A, B) and dogs (C, D). Values are expressed as ratios relative to those of the baseline (pre-administration = 1).

were 1.02 and 0.33, and Cr values were 1.06 and 0.273, respectively. In dogs, the maximum and minimum BUN values were 1.04 and 0.33, and Cr values were 1.15 and 0.29, respectively.

These findings indicate that *Angelica shikokiana* reduced BUN and Cr.

3.2. Study 2

The distribution of cases with values above or below 1 pre-administration and at 30, 90, and 240 days is shown in **Table 1**, and their transitions are illustrated in **Fig. 2**.

Table 1. Distribution of Study 2 data

		Day	0	30	90	240
Dog	BUN	>=1.0	55	50	15	17
(*n*=55)		<1.0	0	5	40	38
	Cr	>=1.0	55	50	16	17
		<1.0	0	5	39	38
Cat	BUN	>=1.0	142	131	30	37
(*n*=142)		<1.0	0	11	112	105
	Cr	>=1.0	142	131	37	37
		<1.0	0	11	105	105

Number of cases with blood urea nitrogen (BUN) and serum creatinine (Cr) values ≥1 or <1 at Days 0, 30, 90, and 240. Values <1 indicate a decrease from baseline.

The maximum and minimum BUN values were 1.03 and 0.30, and Cr values were 1.13 and 0.24, respectively. In dogs, the maximum and minimum BUN values were 1.03 and 0.29, and Cr values were 1.15 and 0.24, respectively.

After 30 days, both cats and dogs were divided into two groups: those maintaining nearly constant values and those showing a decrease. By 90 days, the constant group was further divided into those that remained stable and those that showed a decrease.

At 240 days, the number of cases by stage is shown in **Table 2**. Blood test results are shown in **Fig. 3**, and the statistical results among stages are shown in **Table 3**. In cats, BUN levels were significantly lower in stage 2 than those in stage 3 and in stage 1 than those in stage 2.

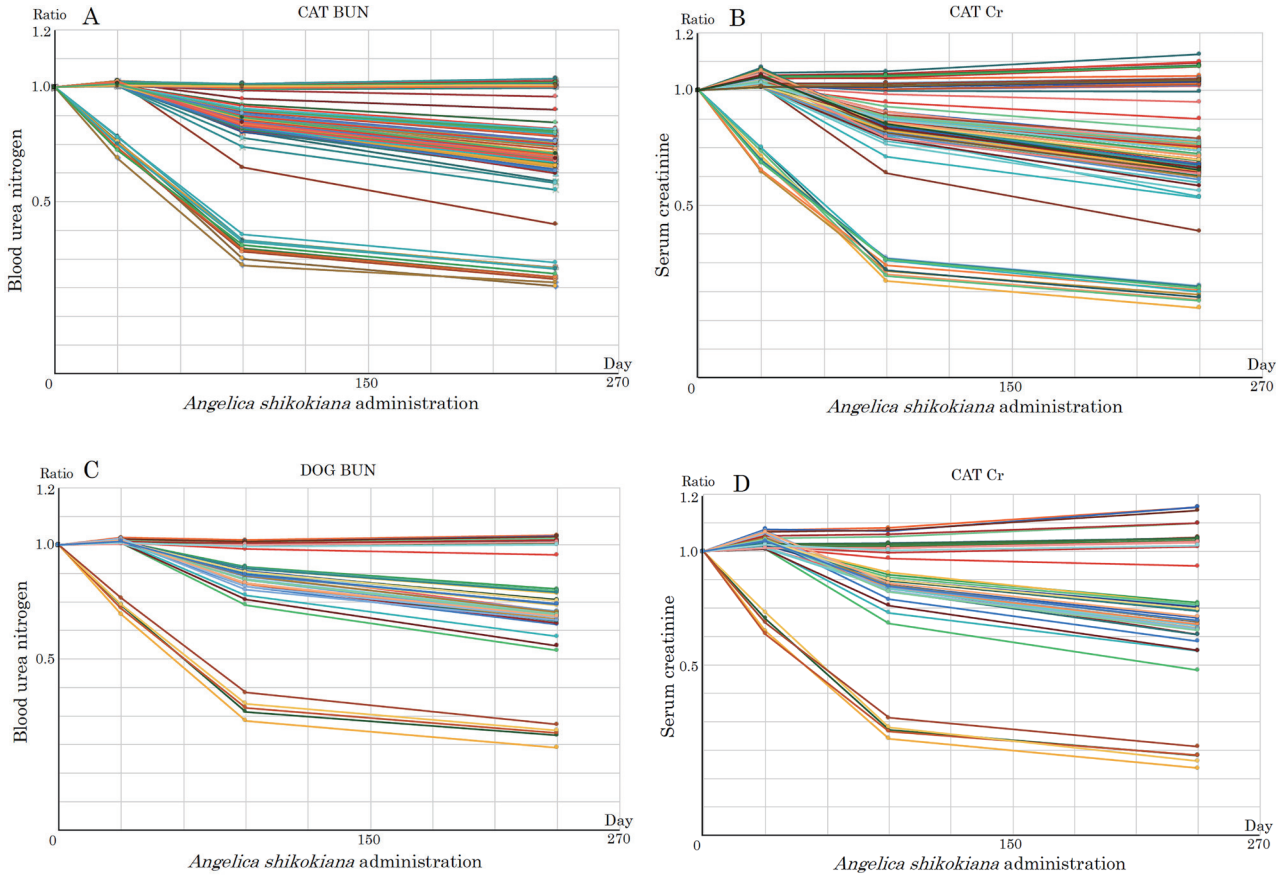

Fig. 2. Blood test results at Day 30, 90, and 240

Changes in blood urea nitrogen (BUN) and serum creatinine (Cr) in cats (A, B) and dogs (C, D). Values are expressed as ratios relative to those of the baseline.

Table 2. Distribution of cases by stage in Study 2

		CKD	BUN level		
		Stage	>=0.9	0.9>x>=0.6	<0.6
BUN	Dog	Stage 1	3	4	0
	(n=55)	Stage 2	2	16	0
		Stage 3	6	6	3
		Stage 4	6	7	2
	Cat	Stage 1	1	18	0
	(n=142)	Stage 2	8	41	0
		Stage 3	11	20	7
		Stage 4	17	14	5

		CKD	Cr level		
		Stage	>=0.9	0.9>x>=0.5	<0.5
Cr	Dog	Stage 1	3	4	0
	(*n*=55)	Stage 2	2	16	0
		Stage 3	6	6	3
		Stage 4	7	6	2
	Cat	Stage 1	1	18	0
	(*n*=142)	Stage 2	8	41	0
		Stage 3	11	21	6
		Stage 4	17	14	5

Classification of cases by renal stage at treatment initiation relative to that of blood urea nitrogen (BUN) and serum creatinine (Cr) values at day 240.

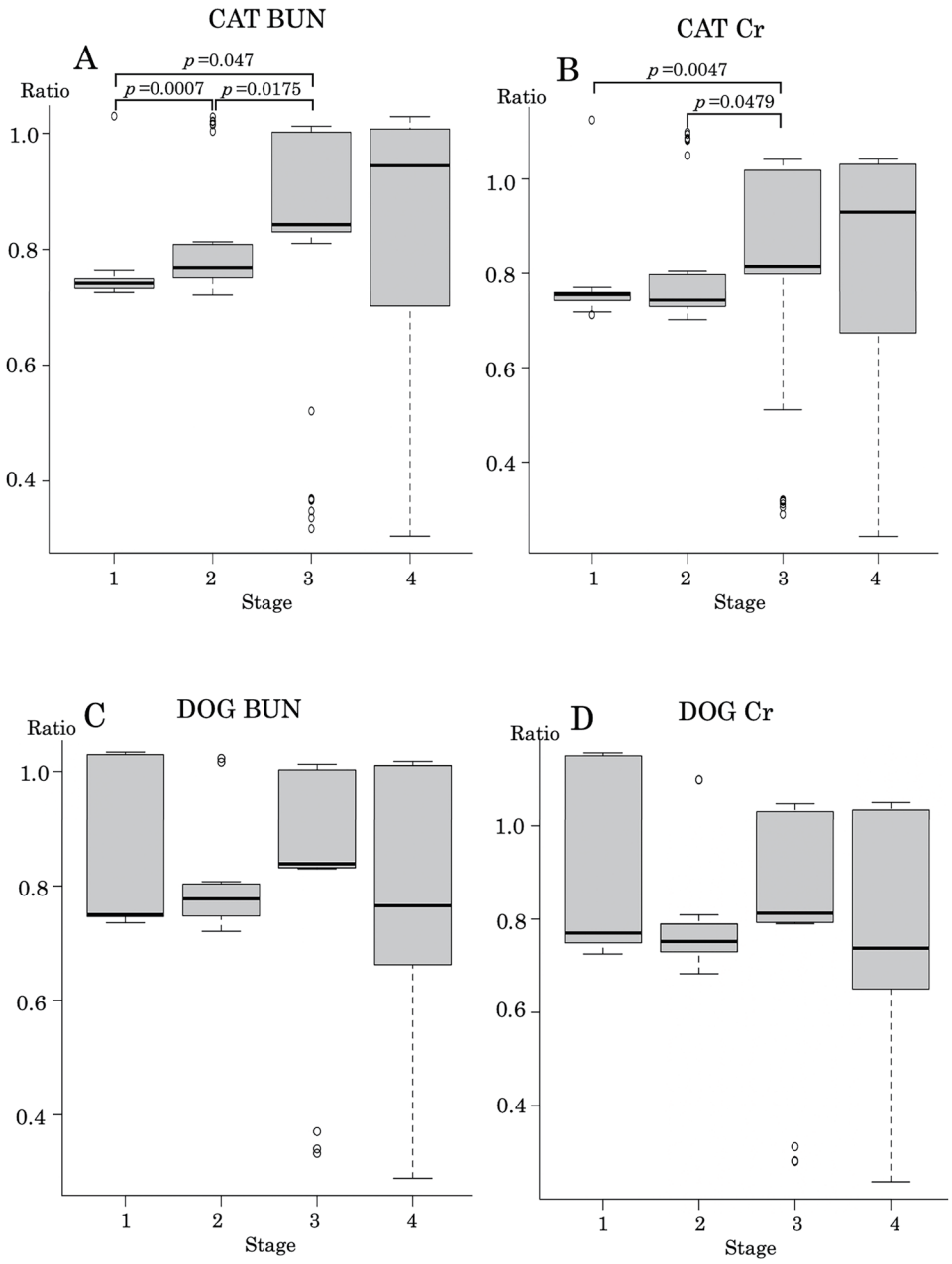

Fig. 3. Comparison by stage classification at Day 240

Ratios relative to those of the baseline are shown on the vertical axes. Significant differences were observed in cats between stages 1 and 2 (p = 0.007), between stage 1 and stage 3 (p = 0.0047), and between stage 2 and stage 3 (p = 0.0175). No significant differences were observed between dogs.

Table 3. Comparison by stage classification at Day 240

Cat	Stage 1:Stage 2	3.8611	**0.0007**
BUN	Stage 1:Stage 3	3.3349	**0.0047**
(*n*=142)	Stage 1:Stage 4	0.6195	0.9259
***p*=0.00695**	Stage 2:Stage 3	2.9353	**0.0175**
	Stage 2:Stage 4	0.3735	0.9822
	Stage 3:Stage 4	0.4434	0.9709
Cat	Stage 1:Stage 2	**0.0205**	1.0000
Cr	Stage 1:Stage 3	3.3364	**0.0047**
(*n*=142)	Stage 1:Stage 4	0.3542	0.9848
p=0.0941	Stage 2:Stage 3	2.5850	**0.0479**
	Stage 2:Stage 4	0.3914	0.9797
	Stage 3:Stage 4	0.1622	0.9985
Dog	Stage 1:Stage 2	0.4237	0.9745
BUN	Stage 1:Stage 3	0.3172	0.9890
(*n*=55)	Stage 1:Stage 4	0.8811	0.8147
p=0.577	Stage 2:Stage 3	2.0608	0.1661
	Stage 2:Stage 4	0.0723	0.9999
	Stage 3:Stage 4	0.0622	0.9999
Dog	Stage 1:Stage 2	1.6351	0.3588
Cr	Stage 1:Stage 3	0.3172	0.9890
(*n*=55)	Stage 1:Stage 4	1.5156	0.4281
p=0.24	Stage 2:Stage 3	1.8805	0.2364
	Stage 2:Stage 4	0.3255	0.9881
	Stage 3:Stage 4	0.6429	0.9180

Significant differences ($p<0.05$, bold) were observed in cats for blood urea nitrogen (BUN) (stage 1 vs. stage 2, stage 1 vs. stage 3, and stage 2 vs. stage 3), and serum creatinine (Cr) (stage 1 vs. stage 2 and stage 1 vs. stage 3).

Similarly, Cr levels were significantly lower in stages 1 and 2 than those in stage 3. Contrastingly, no significant differences were observed between dogs.

Discussion

1. Renal Disease in Small Animals

Renal diseases in dogs and cats are caused by various factors, including hypertension, renal circulatory failure, glomerulonephritis, pyelonephritis, and immune-mediated nephritis.

Renal function is commonly evaluated using blood tests for BUN, Cr, and symmetric dimethylarginine (SDMA) [10–12]. The IRIS staging system for chronic kidney disease is an international standard used to quantitatively assess the decline in renal function and to guide treatment plans and prognosis [8]. First, based on the results of Cr and SDMA, the disease is classified into four stages. Stage 1: Cr is within the normal range, but decreased urine specific gravity, proteinuria, or structural kidney changes on imaging are observed. Stage 2: Mild renal insufficiency with minimal clinical signs. Stage 3: Moderate renal insufficiency, often accompanied by clinical symptoms such as polyuria, polydipsia, and weight loss. Stage 4: Severe renal failure with marked uremic symptoms.

In addition, sub-staging is determined based on proteinuria (urine protein-to-creatinine ratio; UP/C) and blood pressure. For Stage 1–2, dietary management such as a low-phosphorus diet and blood pressure control are recommended. For Stage 3–4, treatment focuses on symptom relief and maintenance of quality of life (QOL) through fluid therapy, antiemetics, and management of anemia. The treatment plan is further refined according to the subf-stage.

However, in the early stages of renal dysfunction, clinical signs (Swelling of the ankles and eyelids, high blood pressure, decreased urine output, proteinuria, frequent urination at night, and loss of appetite caused by uremic toxins, and so on.) other than those of the blood test abnormalities are often minimal, making them difficult for owners to recognize. Schauf *et al*. emphasized the importance of renal protection through moderate protein and phosphorus restriction and lowering the Ca/P ratio in the diet [15]. Consequently, many owners provide renal-supportive diets and supplements such as *Angelica shikokiana*.

2. Components of *Angelica shikokiana*

Angelica shikokiana contains various bioactive compounds. In 1973, Hata *et al*. identified YN-1 as a khellactone-type coumarin derivative [14]. Subsequently, 41 components were isolated from the roots, of which prenylated coumarins promoted insulin secretion [15].

Extracts of *Angelica shikokiana* were reported to significantly reduce amyloid-β25–35-induced neurotoxicity, implicated in neurodegenerative diseases, such as Alzheimer's disease [5]. Additional reported effects include vasodilation [6], improvement of peripheral

circulation and blood pressure regulation [7], prevention of fat accumulation [16], neuroprotection [17], elongation of replicative lifespan of human skin fibroblast [18], inactivation of human immunodeficiency virus [19], suppression of EB virus (EBV) antigen expression leading to potential anti-EBV oncogenic effects [20], and anticancer activity via inhibition of tubulin synthesis [21].

Furthermore, the roots of *Angelica shikokiana* contain abundant arginine and gamma-aminobutyric acid (GABA), suggesting benefits such as anti-fatigue effects, enhanced immunity from arginine, and improved sleep quality from GABA2). The root contains higher levels of YN-1 than those in the leaves, with stronger biological activity [20].

Thus, the diverse effects of *Angelica shikokiana* extracts may contribute to the improvement of renal function through the amelioration of hypertension and renal circulatory impairment.

3. Interpretation of Results

We demonstrated that *Angelica shikokiana* administration reduced the BUN and Cr levels in cats and dogs with renal impairment.

In Study 1, many cats showed decreased BUN and Cr within 0.5 months, and many dogs within 2 months after administration (**Fig. 1**). Some cases did not show improvement (values remaining ≥ 1), although the maximum increases were limited to ~2–5% and 3–15% in cats and dogs, respectively.

In Study 2, the BUN and Cr levels at 240 days were either stable or decreased. Some cases with stable values after 30 d decreased by 90 d. At 240 days, significant improvements in renal function were observed in stage 1 and 2 cats, whereas no significant differences were observed in dogs. This may be partly due to the increasing variability in blood test results with advancing disease stages (stages 1 to 4). However, as shown in **Fig. 2**, many dogs also demonstrated a decreasing trend, suggesting renal benefits in dogs.

Summarily, *Angelica shikokiana* supplementation appears to be useful in maintaining renal function, particularly in cats with early to-moderate renal impairment. To evaluate the renoprotective effects, blood tests should be conducted 30 days after administration. Even if no improvements are observed at that point, supplementation should be continued for at least 90 days before reevaluation.

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Informed Consent

Written informed consent was obtained from the patient for the publication.

Conflict of Interest

None declared.

Data availability

No additional data are available for public disclosure.

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原　著

動物モデルを用いたイヌトウキ（*Angelica shikokiana*）の腎機能改善効果についての検討

林　基弘 (*HAYASHI Motohiro*)[1]*、見立　英史 (*MITATE Eiji*)[2*]

Key Words: イヌトウキ，*Angelica shikokiana*，イソエポキシプテリキシン，YN-1，イソプテリキシン，腎臓病，腎不全

和文要約

イヌトウキ（*Angelica shikokiana*）は，日本固有のセリ科植物であり，その根にはイソエポキシプテリキシン（YN-1）やイソプテリキシンなどのクマリン誘導体をはじめ，各種ビタミン，ミネラル，アミノ酸を豊富に含むことが知られている。

これまでに血糖上昇抑制，抗血小板凝集抑制，神経保護，血管拡張，降圧など多彩な生理作用が報告されている。本研究では，犬および猫における腎機能への影響に着目し，日常診療で得られた血液検査データを用いて後方視的ならびに前方視的に解析を行った。

研究 1 では，猫 56 頭，犬 38 頭を対象に血中尿素窒素（BUN），血中クレアチニン（Cr）の変化を解析した結果，両指標において投与前値を下回る割合が高く，腎機能改善作用が示唆された。

研究 2 では猫 142 頭，犬 55 頭に対して投与前，30 日目，90 日目，240 日目の推移を評価し，特に猫では Stage1 および Stage2 症例において BUN および Cr の有意な低下が認められた。一方，犬において有意差は確認されなかったが，長期投与により腎機能の維持あるいは改善の傾向が見られた。

これらの結果より，*Angelica shikokiana* の継続投与は，特に猫における初期から中等度の腎機能障害症例に対し有効である可能性が示された。したがって，腎機能維持を目的とした日常的なサプリメント投与は有用であり，少なくとも 90 日間の継続評価が望ましいと考えられる。

*** 責任著者：**見立　英史 (Eiji Mitate) [2]

所属機関

[1] 林技研株式会社（〒 160-0021　東京都新宿区歌舞伎町 2-3-21-606）

[2] 金沢医科大学医学部顎口腔外科（〒 920-0265 石川県河北郡内灘町大学 1-1）