Successful Management of Hepatopathy in a Labrador Retriever Using Western Herbal Medicine

Dr Kimberly Schmidt, USA, DVM, CVA, CVCH, CVFT, GDipVWHM

ABSTRACT:
A Western herbal tincture of Astragalus membranaceous, Bupleurum falcatum, Cynara scolomus, Rehmannia glutinosa and Corydalis ambigua was successfully used to manage Chronic Idiopathic Hepatopathy in a 12yo F/S Labrador Retriever. After one month on the herbal formula the patient's alanine aminotransferase decreased to within the reference range and the alkaline phosphatase was reduced by 42%, and after five months by 50%. The patient also experienced symptom improvement including more energy, more activity, a decrease in pain and resolution of coughing.

WESTERN MEDICAL HISTORY:
The patient presented for routine lab work to her general veterinarian on March 12, 2021 after her owner noticed a mild increase in water intake and panting (see Table 1 in Addendum for pertinent values). Elevated liver enzymes were found, with alanine aminotransferase being 126 U/L and alkaline phosphatase being 416 U/L.

Bloodwork and urinalysis initially performed on 6/11/16 was within normal limits, other than isosthenuric urine with a USG of 1.007, no protein detected at that time. The patient had bilateral TPLO surgery 3/15/16 with an orthopedic surgeon. She also had a history of limping on the front right leg since early June 2017, radiographs revealed very mild osteoarthritis of the right elbow. Meloxicam was prescribed for as needed use by her general veterinarian on a regular basis, starting 1/17/16 and was continued until 1/19/22.

The patient had also been on Phenylpropanolamine 50mg PO BID since early 2016. On 7/15/21 her owner reported urinary incontinence while taking this dose. An in-house urinalysis revealed 30mg/dL protein and was otherwise unremarkable. She was switched to Estriol 1mg PO SID weaning down to lowest effective frequency to control urinary incontinence. On 9/19/21 she began to have mild urinary incontinence again while still on Estriol 1mg PO SID and Phenylpropanolamine 50mg PO SID was added in addition, which resolved the incontinence. On 11/22/21 she was noted to have more urinary incontinence and Phenylpropanolamine was increased to 50mg PO BID. Estriol was continued as well at 1mg PO SID.

Bloodwork and urinalysis was repeated 1/14/22 (see Table 2 for pertinent values). Alkaline phosphatase had increased to 1,894 U/L and ALT to 319 U/L. Cholesterol was also elevated at 377mg/dL. Although USG was slightly higher at 1.016, 3+ proteinuria was present. An abdominal ultrasound was performed in house at the general veterinarian on 1/19/22 (see ultrasound report Addendum 1). The liver was noted to be hyperechoic and mottled in texture with nodular hyperplasia appreciated in the left liver. An ACTH stimulation test was performed 1/19/22 and was within reference range. A UPC was also performed and was elevated at 3.8. A urine culture was not performed at the time. The patient was started on Denamarin 225mg 2T PO SID and Amoxicillin/Clavulanic Acid 375mg 1T PO BID. Meloxicam was discontinued at this time.

Repeat urinalysis was performed 2/5/22 and proteinuria was stable at 3+ with a USG of 1.012. UPC at that time was increased at 6.4. Bloodwork was also repeated (see Table 3 for pertinent values). Although ALT had decreased slightly, ALKP had increased. Denamarin and Amoxicillin/ Clavulanic Acid were discontinued and referral was made at that time.

The internal medicine specialist first saw the patient on 3/31/22. Blood pressure was taken with a #4 cuff on the right posterior limb with Doppler and was 200mmHg systolic. Three view thoracic radiographs were performed and revealed a mild diffuse bronchointerstitial pattern with mild

generalized cardiomegaly. Bloodwork was repeated (see Table 4 for pertinent values). Antinuclear Antibody testing was negative. Abdominal ultrasound at that time by the internist showed an irregular, lobulated smaller liver with a hypoechoic hepatic nodule and left chronic renal change (see Addendum 2 for ultrasound report). The patient was started on Telmisartan 20mg PO SID, Clopidogrel 75mg 1/2T PO SID and Amlodipine 5mg 1T PO SID. Fish oil was also recommended at a dose of 2,000mg combined EPA/DHA long term. It was recommended that Phenylpropanolamine be discontinued. Estriol was continued but was increased to 1.5mg PO SID. A slow transition to a prescription renal diet was recommended.

The patient returned for a re-check with the internist on 4/12/22. Blood pressure was decreased (see Addendum 3 for results). Bloodwork was also performed and showed a decrease in ALT but an increase in ALKP and Cholesterol (see Table 5 for pertinent results). UPC had decreased to 1.2. Modified Cyclosporine 100mg PO SID was started on 4/15/22 due to the increasing liver enzymes.

The patient re-checked again on 5/17/22 for Bloodwork (see Table 6 for pertinent values). ALKP had increased slightly but ALT had decreased to normal. Cholesterol was within normal limits at this visit. Her hematocrit had decreased significantly to 38.8% but was still within reference range. All current medications were continued at that time.

She presented for another re-check with the internist on 7/14/22. Her owner noted that she had some muscle fasciculation ("shivering") events which started in May of 2022 and they had been getting worse. Bloodwork and urine was repeated (see Table 7 for pertinent values). Her alkaline phosphatase had increased significantly to 2,371 U/L and her ALT was slightly increased at 157 U/L. Cholesterol was mildly elevated again. A low dose dexamethasone suppression test was done on 7/20/22 and was within normal limits (see Table 8 for results). Blood pressure was taken with a #5 cuff on the right posterior limb with an oscillometric machine and had decreased to 111/75 (88) mmHg. Treatment was kept the same and a re-check was scheduled in four months. The patient then presented to Napa Valley Holistic Veterinary Services on 9/1/22 for a holistic consultation.

WESTERN DIAGNOSIS:

The patient had a long standing history of urinary incontinence, even prior to the earliest records that could be obtained in 2016. She also had a history of torn anterior cruciate ligaments bilaterally with subsequent bilateral tibial plateau leveling osteotomies of both hindlimbs in 2016. She also had mild osteoarthritis of the right front elbow diagnosed in 2017. A diagnosis of glomerulonephritis, protein losing nephropathy and chronic idiopathic hepatopathy (suspect hepatitis) were given by the internal medicine specialist on 3/30/22. The patient was also diagnosed with hypertension and hypercholesterolemia. Liver biopsies were not discussed in the medical record at the time of the internal medicine visit and treatment was instituted with medications. Based on radiographs in March of 2022 the patient also had mild generalized cardiomegaly and a mild diffuse bronchointerstitial pattern of unknown etiology. Laryngeal paralysis was suspected by the internist based on her increase in panting and mild stridor. A mild, non-regenerative anemia was later diagnosed.

INTEGRATIVE EVALUATION:

The patient was seen on 9/1/22 for a holistic evaluation and herbal consultation. The owner reported her appetite to be great. Her stools were occasionally soft. Energy level was low. She did report an occasional cough, more of a "throat clearing" as she described it. Urinary incontinence was not present. Water consumption was increased. Her weight had also increased when she transitioned on the new dry prescription renal diet Royal Canin Renal Support A. Her owner also reported muscle fasciculations "shivering" as she called it, especially after swimming. This was attributed to physical discomfort.

On physical examination the patient was 28.6kg. Her capillary refill time was one second. Gums were pink and moist. Heart rate was 130bpm. She was panting with mild stridor. Her BCS was 6/9. Ophthalmic examination was within normal limits. Ears were warm throughout and her head was

slightly warm. External otic exam was within normal limits. Her tongue color was dark red and dry. Pulses were deep and weak on the left and superficial on the right, and slightly bounding. Lymph nodes and abdominal palpation were normal. No lameness was noted on this initial visit. Daisy had been receiving acupuncture and cold laser therapy by another veterinarian in the holistic practice since February 22, 2021. Conscious proprioception was normal. Her vulva was hooded but appeared normal. Coat was good but nails were long, especially in the front.

From a TCVM perspective the patient was diagnosed with Liver and Kidney Yin Deficiency based on her warm ears and head, increased panting and increased water intake, as well as her red and dry tongue and weaker, deeper pulses on the left with superficial pulses on the right.

INTEGRATIVE TREATMENT:
Prior to holistic evaluation for an herbal consultation the patient's pain had been managed with acupuncture and cold laser therapy. Her glomerulonephritis was managed with Telmisartan 20mg PO SID, Clopidogrel 75mg 1/2T PO SID and Amlodipine 5mg 1T PO SID as well as a dry prescription renal diet. Her hepatopathy was managed with Cyclosporine 100mg PO SID. Urinary incontinence was controlled with Estriol 1.5mg PO SID. Supplements at the time of the holistic evaluation were Standard Process Ligaplex II 2 capsules PO BID, which she had been on since her TPLO surgeries in 2016. She was also taking fish oil 2,160mg EPA + DHA daily. She was on a joint supplement, Dasuquin 1T PO SID, Adequan 1.3mL SQ monthly, a probiotic, Proviable DC 1c PO SID and Heartgard and NexGard for monthly flea, tick and heartworm prevention.

The patient was started on a Western herbal tincture with the following goals:

1. Prevent glomerular sclerosis and decrease glomerular inflammation to reduce proteinuria
2. Decrease inflammation and relieve arthritis pain to allow more activity and improve comfort
3. Detoxify and support healthy digestion and elimination to improve liver dysfunction

A Western herbal tincture was started as follows as a dose of 4mL PO BID.
Astragalus membranaceous 1:2 70mL
Bupleurum falcatum 1:2 50mL
Cynara scolymus 1:2 30mL
Rehmannia glutinosa 1:2 50mL
Corydalis yanhusuo 1:4 50mL

Astragalus membranaceous was used for its anti-inflammatory, hypotensive, renoprotective and adaptogenic effects. It has been shown to decrease proteinuria in clinical trials (Zhang et al., 2014). Ahmed et al. (2007) showed it's effectiveness in treating nephropathy and nephrotic syndrome in people.. Astragalus membranaceous has also been shown to help reduce blood pressure in animal models (Chen et al., 2003). Bupleurum falcatum was used for it's anti-inflammatory, hepatoprotective, analgesic and cooling effects. It is also useful for decreasing 'shivers'. Bupleurum falcatum has been shown to be nephroprotective in animal models (Chen et al., 2008).

Cynara scolymus was used as a digestive bitter to improve digestion and elimination as an alterative. It is also a known choleretic and cholagogue, increasing liver function and elimination. It is hepatoprotective and hepatorestorative, particularly indicated for a chronic hepatopathy with a small liver on ultrasound. It has also been reported to reduce liver enzymes in human patients (Amini, 2022).

Rehmannia glutinosa was used as an anti-inflammatory and cooling agent. Lee et al. (2009) illustrated in a clinical trial that Rehmannia glutinosa has a renoprotective effect.

Corydalis ambigua was used for it's analgesic properties, which have been discussed by Alhassen, et al. (2021). It is also a hypotensive and is cardioprotective, since the patient did have hypertension as well

as mild generalized cardiomegaly, cardiac support was desired.

The daily dose of each herbal was as follows:

Astragalus membranaceous 1:2 dosed at 2.3mL per day (1g per 2mL = 0.5g per mL = 1.15g in 2.3mL). 1.15g x 1,000 = 1,150mg. Daily dose = 1,150mg/28.6kg = 40.2mg/kg.

Bupleurum falcatum 1:2 dosed at 1.7mL per day (1g per 2mL = 0.5g per mL = 0.85g in 1.7mL). 0.85g x1,000 = 850mg. Daily dose = 850mg/28.6kg = 29.7mg/kg.

Cynara scolymus 1:2 dosed at 1.1mL per day (1g per 2mL = 0.5g per mL = 0.55g in 1.1mL). 0.55g x 1,000 = 550mg. Daily dose = 550mg/28.6kg = 19.2mg/kg.

Rehmannia glutinosa 1:2 dosed at 1.7mL per day (1g per 2mL = 0.5g per mL = 0.85g in 1.7mL). 0.85g x1,000 = 850mg. Daily dose = 850/28.6kg = 29.7mg/kg.

Corydalis yanhusuo 1:4 dosed at 1.7mL per day (1g per 4mL = 0.25g per mL = 0.425g in 1.7mL). 0.425g x1,000 = 425mg. Daily dose = 425/28.6kg = 14.86mg/kg.

Herb-drug interactions were also explored. The hypotensive effects of Bupleurum falcatum, Cynara scolymus and Corydalis yanhusuo could potentially compound the hypotensive effects of Telmisartan and Amlodipine, however it was also noted that they could possibly assist in lowering blood pressure and medication doses long term. Rehmannia glutinosa can induce CYP3A4 which may cause a decrease in Cyclosporine levels, so monitoring levels was recommended. Astragalus membranaceous can inhibit CYP3A4, potentially increasing Cyclosporine levels, so monitoring levels was recommended. It should be noted that this was communicated to the internist, who stated that she doesn't recommend monitoring Cyclosporine levels unless signs of toxicity are evident.

In addition to the recommended herbal treatment, a diet change was recommended to a whole fresh renal diet (Just Food For Dogs Renal Support Low Protein). It had a similar maximum protein content on a g/MCal basis (46g/MCal) as the Royal Canin Renal Support A (45g/MCal). This change was also communicated to her internist, who was supportive.

The patient was seen again by our holistic practice on 9/28/22. Her appetite was great and she was taking the herbal formula in her food. Stools were still soft sometimes. Her energy level had improved and was noted to be pretty good. The owners did state that she had escaped and roamed around the property, so she seemed to be feeling better overall. No coughing had been noted. The patient was drinking less water overall and there were no urinary issues. She seemed to be less painful and more comfortable per the owner. No shivering had been noted since the last visit. On physical examination her tongue was slightly red and moist, ears were warm throughout. Her pulses were a little superficial and slightly choppy bilaterally. She was panting with mild stridor. She had a very mild limp on the right forelimb (grade 2/5). She had mild back discomfort at the acupuncture points BL 18, BL 19 and BL 20 bilaterally. Physical exam was otherwise unremarkable.

All herbs were continued at the same dose except the Corydalis yanhusuo, which was increased to help with her musculoskeletal pain that was noted on examination. The dose was increased to 2.3mL per day, which is equivalent to 575mg (20mg/kg). The total dose of the formula was therefore increased to 4.5mL PO BID.

Blood pressure was performed at the patient's general veterinarian on 9/22/22 and was 128-138mmHg systolic. The patient was seen for a re-check at her internist and bloodwork and urine were performed on 10/25/22. See Table 9 for pertinent values. ALT had decreased to within reference range and ALKP had decreased by 42%. Cholesterol and lipase had also decreased to within reference range. Hematocrit, although just slightly lower, was now a documented mild, non-

regenerative normocytic hypochromic anemia.

The patient was seen again at our holistic practice on 12/8/22. Her appetite was great. She had one episode of vomiting the night before, which was attributed to dietary indiscretion. Stools were still occasionally soft. Energy level was reported to be great. She had been very active and comfortable. No coughing was noted. She had transitioned fully to the whole fresh renal diet and was now a normal body condition of 5/9 at 26.6kg. Water intake was normal. No shivering had been noted, even when she was swimming recently. Panting was noted to be decreased. She had developed a suspected tooth root abscess and antibiotics were started (Cephalexin 750mg PO BID). On physical exam tongue was slightly pale and moist. There was a firm facial swelling on the nasal bridge over 108, which was noted to be fractured with sensitive gingival mucosa overlying. Ears were warm throughout. Pulses were a little choppy but even bilaterally. Breathing was eupneic. No lameness was noted on exam and although mild back discomfort was present it was improved from the previous visit. The same herbal formula was continued.

The patient was seen again at the internist on 2/10/23. Bloodwork and urine were performed. See Table 10 for pertinent values. Anemia had resolved. Although ALKP was elevated it was decreased from the previous visit and by 50% overall. ALT was well within reference range.
Cholesterol and lipase were also within normal limits. Cyclosporine dosage was decreased by 25% to 75mg PO SID.

DISCUSSION:
This case report represents an excellent example of how integrative therapy can used to be manage multiple complicated medical conditions in a patient. It also illustrates the cooperation between the herbalist and the internist to successfully manage the patient and decrease her medication doses over time, while improving not only her labwork values, but also her pain, mobility, energy and vitality.

The initial medical management by the internist was quite successful in decreasing her blood pressure and lowering her urine protein:creatinine ratio and proteinuria. However, the patient's alanine aminotransferase and alkaline phosphatase remained high, as well as her cholesterol and lipase. In addition, her clinical evaluation showed lethargy and discomfort (illustrated by shivering), with an increase in panting and sustained polydipsia. After herbal treatment the patient's energy was greatly improved, as well as her mobility and stamina. Her discomfort had resolved and no further shivering was noted.

By incorporating a Western herbal formula, we were also able to balance the patient energetically. Cooling herbs such as Bupleurum falcatum and Rehmannia glutinosa were used to clear the excess heat. After subsequent visits the patient was panting less and drinking less water. Her tongue was also noted to be less red and more moist, all indicators of heat clearing.

The herbal formula was also successful in lowering her liver values. ALT decreased to well within the reference range and ALKP was greatly reduced (42% after one month on herbs and 50% after five months on herbs). The chronic idiopathic hepatopathy was successfully managed with herbal therapy.

I also thought it interesting to note that the patient's cough resolved with herbal therapy. I have several theories on why this may have occurred. Bupleurum falcatum is an anti-inflammatory that is used in disorders of the upper respiratory tract. It is also useful for asthma and chronic cough, so this may have been an effective part of the formula for alleviating cough in this patient.
Rehmannia glutinosa is another anti-inflammatory herb that is useful for asthma. In addition Astragalus membranaceous is an immunomodulator and anti-inflammatory agent, which may have assisted in decreasing cough through anti-inflammatory and immune modulating mechanisms. It also may have been a combination of these therapies. Although this was not an intended effect of the formula, it was a beneficial outcome.

The patient did have a significant drop in Hematocrit after starting Modified Cyclosporine therapy. This may have been due to anemia of chronic disease, however, anemia has been a reported side effect of systemic cyclosporine therapy in humans (Palestine, Nussenblatt and Chan, 1984).. It will be interesting to note was happens with the Hematocrit as the patient weans off of Cyclosporine therapy in the future.

Perpetuating factors in this case predisposing to immune dysfunction and leading to glomerulonephritis and hepatopathy may have been chronic Meloxicam usage over time, leading to direct organ damage and also gut dysfunction which in turn disrupted the immune system.
Also the chronic intake of dry dog food, promoting inflammation in the body may have been a perpetuating factor.

Table 1 (Bloodwork 3/12/21):

Test	Result	Reference Range
Albumin	3.4 g/dL	2.7-3.9
ALKP	416 U/L H	5-160
ALT	126 U/L H	18-121
BUN	14 mg/dL	9-31
Creatinine	0.8 mg/dL	0.5-1.5
SDMA	14 ug/dL	0-14
HCT	46.9%	38.3-56.5

Table 2 (Bloodwork and Urinalysis Results 1/14/22):

Test	Result	Reference Range
Albumin	3.2 g/dL	2.7-3.9
ALKP	1,894 U/L H	5-160
ALT	319 U/L H	18-121
Cholesterol	377 mg/dL H	131-345
BUN	23 mg/dL	9-31
Creatinine	0.7	0.5-1.5
SDMA	10 ug/dL	0-14
HCT	50.9%	38.3-56.5

USG	1.016	N/A
Proteinuria	3+ H	N/A
aaaa		

Table 3 (Bloodwork 2/5/22):

Test	Result	Reference Range
Albumin	3.2 g/dL	2.2-3.9
ALKP	1,907 U/L H	23-212
ALT	243 U/L H	10-125
BUN	12 mg/dL	7-27
Creatinine	1.0 mg/dL	0.5-1.8
PCV	69% H	N/A

Table 4 (Bloodwork and Urine 3/3122):

Test	Result	Reference Range
Albumin	2.9 g/dL	2.7-3.9
ALKP	1,238 U/L H	5-160
ALT	149 U/L H	18-121
Cholesterol	354 mg/dL H	131-345
Lipase	264 U/L H	0-250
UPC	6.5 H	<0.2
USG	1.011	N/A
Proteinuria	3+ H	N/A
HCT	49.8%	38.3-56.5

Table 5 (Bloodwork and Urine Results 4/12/22):

Test	Result	Reference Range

Albumin	3.2 g/dL	2.7-3.9
ALKP	1,683 U/L H	5-160
ALT	170 U/L H	18-121
Cholesterol	424 H	131-345
UPC	1.2 H	<0.2
USG	1.010	N/A
Proteinuria	2+ H	N/A
HCT	48.3%	38.3-56.5

Table 6 (Bloodwork 5/17/22):

Test	Result	Reference Range
SDMA	23 microgram/dL	0-14
ALKP	1,777 U/L H	5-160
ALT	120 U/L	18-121
Cholesterol	337 mg/dL	131-345
HCT	38.8%	38.3-56.5

Table 7 (Bloodwork and urine 7/14/22):

Test	Results	Reference Range
Albumin	3.5 g/dL	2.7-3.9
ALKP	2,371 U/L H	5-160
ALT	157 U/L H	18-121
Cholesterol	350 H	131-345
HCT	38.8%	38.8-56.5
USG	1.008	N/A
Proteinuria	1+ H	N/A
UPC	0.9 H	N/A

Table 8 (Low Dose Dexamethasone Suppression Test 7/20/22):

Test	Results	Reference Range
Cortisol - Baseline	3.6 microgram/dL	1-6
Cortisol - 4 hr Post Dex	0.3 microgram/dL	
Cortisol - 8 hr Post Dex	1.5 microgram/dL	

Table 9 (Bloodwork and Urine 10/25/22):

Test	Results	Reference Range
ALKP	1,357 U/dL H	5-160
ALT	95 U/dL	18-121
Cholesterol	317 mg/dL	131-345
Lipase	145 U/dL	0-250
HCT	37.7%	38.3-58.5
USG	1.005	N/A
Proteinuria	Negative	N/A

Table 10 (Bloodwork and Urine 2/10/23):

Test	Results	Reference Range
HCT	39.9%	38.3-56.5
ALKP	1,163 U/L H	5-160
ALT	74 U/L	18-121
Cholesterol	341 mg/dL	131-345
Lipase	141 U/L	0-250
USG	1.008	N/A
Proteinuria	Negative	N/A

Addendum 1 (Ultrasound Report 1/19/22):

Ultrasound- Liver appears hyperechoic and mottled. No loss of normal architecture. Nodular hyperlasia is appreciated in Left side of liver; which had normal liver tissue appearance. Gall bladder is enlarged, anechoic fluid (anorexic). Spleen normal appearance, and normal kidney appearance. Bladder is full with anechoic fluid. L adrenal was located and not enlarged (0.5cm caudal pole), R

adrenal could not be definatively identified. R cranial abdo had a 1cm anechoic structure that did not have blood flow on flow ultrasound. Did not appear to be R adrenal, suspect LN.

Addendum 2 (Ultrasound Report 3/30/22):

The liver is small in size with an irregular margin and mottled architecture. There is a hypoechoic nodule ventral to the gallbladder (1.5x1.5cm). The gallbladder is normal containing anechoic fluid with no common bile duct dilation noted. Normal wall thickness. The stomach has a normal gas pattern and normal wall layering. The pancreas is smooth and normal in size.

The spleen is normal in size, shape and echogenicity and no focal lesions are appreciated. The left kidney measures 6.5 x 3.62 with normal shape but poor corticomedullary distinction. The right kidney measures 6.74 x 3.42 with a normal shape and appropriate corticomedullary distinction. The left adrenal gland measures 0.65 with normal shape and size. The right adrenal gland measures 0.65 with normal shape and size. The urinary bladder has normal contour and thickness with no overt obstructions, uroliths or masses noted. The intestinal tract has normal bowel wall layering and gas pattern. Abdominal lymph nodes were not visualized. No free fluid was present.

Addendum 3 (Systolic blood pressure results 4/12/22):

Size #4 cuff right posterior limb via Doppler 150 mmHg
138 mmHg
138 mmHg
140 mmHg
140 mmHg

REFERENCES:

AHMED et al. (2007) Treatment of idiopathic membranous nephropathy with the herb Astragalus membranaceus. American Journal of Kidney Disease. 50(6) 1028-1032.

ALHASSEN et al. (2021) The Analgesic Properties of Corydalis yanhusuo. Molecules. 26(24). 7498.

AMINI, K. (2022) Effects of Artichoke Supplementation on Liver Enzymes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clinical Nutrition Research.
11(3). 228-239.

CHEN et al. (2003) Effect of Astragalus membranaceus on baroreflex sensitivity in spontaneously hypertensive rats. Zhongguo Zhong Yao Za Zhi. 28(2) 155-158.

CHEN et al. (2008) Effects of Bupleurum scorzoneraefolium, Bupleurum falcatum, and saponins on nephrotoxic serum nephritis in mice. Journal of Ethnopharmacology. 116(3) 402.

LEE, B. et al. (2009) Rehmannia glutinosa ameliorates the progressive renal failure induced by 5/6 nephrectomy. Journal of Ethnopharmacology. 122(1). 131-135.

PALESTINE, A.G, NUSSENBLATT, R. B., CHAN, C. C. (1984) Side effects of systemic cyclosporine in patients not undergoing transplantation. American Journal of Medicine. 77(4) 652-656.

ZHANG et al. (2014) Astragalus (a traditional Chinese medicine) for treating chronic kidney disease. Cochrane Database of Systematic Reviews. [Online]. Cochrane Database. (10) Available from https://www.cochranelibrary.com/cdsr/doi/ 10.1002/14651858.CD008369.pub2/full.