

A Case Control study to assess the Etiologic Risk factors, Incidence and Prevalence of Nephrolithiasis in South India

Jobin Kunjumon Vilapurathu^{1,2}, G. R Vijaya Sankar^{1*}, B.S Venkateswarlu¹, Margret Chandira¹, S. Shanmuganathan³

*¹Department of Pharmacy, Vinayaka Mission's College of Pharmacy, Vinayaka Mission Research Foundation-Deemed to be University (VMRFDU), Sankari Main Road, Ariyanoor, Salem-663008, Tamil Nadu, India.

²Department of Pharmacy Practice, Nirmala College of Pharmacy, Muvattupuzha P.O, Muvattupuzha, Kerala 686661, India

³ School of Pharmacy, Sri Balaji Vidyapeeth, SBV Campus, Pillaiyarkuppam, Pondicherry - 607402, India

CORRESPONDING AUTHOR

Dr. G. R Vijaya Sankar

Department of Pharmacy, Vinayaka Mission's College of Pharmacy, Vinayaka Mission Research Foundation-Deemed to be University (VMRFDU), Sankari Main Road, Ariyanoor, Salem-663008, Tamil Nadu, India. Email: vijayasankar95@gmail.com

Abstract

Objective: To evaluate the etiologic risk factors and prevalence associated with Nephrolithiasis in South Indian Population

Materials & Methods: Case controlled study to analyze the risk factors of Nephrolithiasis was carried out at a Tertiary care Hospital in Kerala. The details of 1290 patients between the age group 20 to 90 years who were diagnosed with Nephrolithiasis during the study period was compared with gender and age matched control who came to the hospital on the same day. The study participants included both In-patients and out patients. The patient details were collected and analyzed for various risk factors which can lead to the formation and recurrence of Nephrolithiasis.

Results: The study population mean age group of 53.14±15.33, most of the subjects falling between the age group between 51-60 years. About 75% of the patients who were included in the study had previous history of Nephrolithiasis with the last confirmed symptomatic episode within 1 year of the study (Mean being 10± 4 months). The main dietary risk factors which were identified was Calcium and purine rich foods (CI=95%, P<0.001), Alcohol, Obesity and Lack of exercise was also found to be having significant correlation in the incidence and recurrence of the condition.

Conclusion: Analyzing the data obtained it can be concluded that elderly and obese patients are more prone for recurrence of Nephrolithiasis. The dietary habits of the patients had a significant impact in the incidence and recurrence of nephrolithiasis. The regular inclusion of foods rich in Calcium oxalate, uric acid and purine can increase the severity of the condition. Decreased fluid intake along with life style risk factors such as lack in exercise, smoking, obesity and Alcohol intake can also increase the chance for Nephrolithiasis. Diabetes, Hypertension and Hyperlipidemia were the most significant comorbidities evident in Nephrolithiasis patients.

Key Words: Nephrolithiasis, Kidney Stone, Calcium Oxalate, Uric acid, Struvite, Cysteine

INTRODUCTION

Nephrolithiasis also termed as Renal Calculi or Kidney stones can be defined as a condition in which stones are formed due to the supersaturation of urine in any anatomical region of the kidney.^{1,2} The size of the stone can range from tiny to staghorn stones.³ Globally, it is one of the most widespread clinical disorders affecting up to 12% of the population.^{4,5} Nephrolithiasis is very prevalent in certain geographic locations such as United States, South Africa, India and other South East Asian Countries.^{6,7,8} It is found to be having high incidence in parts of south India.⁹ This Geographical incidence can be attributed to the variations in climate especially humidity, intensity of heat and level of water consumption and the

dietary habits.¹⁰ The location in which the stones can be formed may vary and the most common areas being ureter, Kidney, bladder, Pelvic Ureteric Junction (PUJ) and Vesicoureteral Junction (VUJ).^{11,12} It is usually formed due to the supersaturation of any substance and the most prominent types of stones include Calcium, Uric acid, Struvite and Cysteine.^{13,14,15}

Patients and Methods

The present study was designed as a Case control study in which the dietary habits and lifestyle risk factors of Nephrolithiasis patients who reported in a tertiary care hospital in Kerala were compared with a control group.

After obtaining sufficient ethical clearance from Institutional Human Ethics Committee (08/IHEC/07/2020/NCP) the study was conducted at the Emergency, Surgical and Urology Department of a tertiary care Hospital. The Inclusion criteria for the case group was a confirmed diagnosis of Nephrolithiasis and between the age group of 18-90 years. Patients having any history of malignancy or autoimmune conditions were excluded. Pregnant and lactating women were also not included in the study. Age and gender matched control group were also selected along with the cases. During the study period, 1290 patients who were having confirmed diagnosis of Nephrolithiasis were included in the Case group while 1290 patients who reported to hospital for some other conditions and not having any confirmed diagnosis of Nephrolithiasis was chosen into the control group. Both groups were informed about the study and consent for the participation in the study was obtained. Specially designed Data Collection was utilized to obtain the information on various dietary habits, Life style risk factors and comorbidities of both the groups. The obtained data was categorized and analyzed for chances of risk factors which can lead to the incidence and recurrence of Nephrolithiasis. Risk factor analysis and their strength of association was calculated using Odds Ratio.

RESULTS AND DISCUSSION

Kidney stone is a medical condition in which small hard deposit of acid salts and minerals adhere together in the supersaturated urine that is formed in the kidney. These stones may either be confined in the kidney or will be transported down to the ureter which may lead to a lot of discomfort to the individual. Long standing

nephrolithiasis can also lead to a variety of discomforts to the individuals such as recurrent Urinary tract infections, progressive kidney disease and so on. This case control study in patients with nephrolithiasis revealed the prevalent age group, sex, lifestyle risk factors and food preferences, comorbidities connected with Nephrolithiasis and its risk of recurrence.

Prevalence of Nephrolithiasis among study Population

A total of 1290 patients having a confirmed diagnosis of nephrolithiasis were enrolled in the case arm while 1290 age and gender matched persons not having kidney stone was enrolled to the control arm. During the study, it was observed that the enrolled Nephrolithiasis patients had a mean age group of 53.14 ± 15.33 years. The most predominant age group was between 51-60 years. The gender analysis reveals that mainstream of the patients in the study was males 59.37%. This is in accordance with Khaling Mikawlawng et al.,¹⁸ who conducted a study in 875 Nephrolithiasis patients in Manipur and reported that urolithiasis is significantly 109 (56.7%) observed in individuals in the age group of 45 to 60 years. The study also reported that in case of urolithiasis, males are more affected than females. Within the 1290 patients enrolled to the case arm 966 patients (74.89%) had previous history of Nephrolithiasis. A study conducted by Ross Morton et al.,¹⁹ points out that urolithiasis is having a lifetime recurrence rate of 60%–80%. This being an important risk factor associated with the recurrence of the condition was further analyzed to determine the number of prior episodes of Nephrolithiasis before this admission which is given in Table 1

Number of Episodes	Nephrolithiasis Patients (N=966)	
	Number	Percentage
1	554	57.34%
2	204	21.11%
3	151	15.63%
≥4	57	5.90%

Table 1: Gives the number of confirmed prior symptomatic episodes of Kidney Stone

The analysis of the number of prior symptomatic episodes of kidney stone the patients had undergone reveals the majority were having only one prior episode (57.34%) and

the most of them had experienced this event within one year before this study, the mean period before the last confirmed symptomatic episode being 10 ± 4 months.

Comorbidity	Number of Patients	Percentage
Type II Diabetes Meletus	154	11.93%
Hypertension	243	18.83%
Dyslipidemia	113	8.76%
Coronary Artery Disease	2	0.15%
Type II DM + Hypertension	282	22.32%
Type II DM + Dyslipidemia	45	3.48%
Type II DM + CAD	99	9.14%
Hypertension+ DLP	41	3.17%

Hypertension+ CAD	39	3.02%
Type II DM + Hypertension+ DLP	19	1.87%
Type II DM + DLP + CAD	17	1.31%
Type II DM + Hypertension+ CAD	37	2.86%
Hypertension+ DLP+CAD	21	1.62%
Type II DM + Hypertension+ DLP+CAD	11	0.85%
No Comorbidities	167	12.94%

Table 2: Shows the comorbidities associated with Nephrolithiasis

In Table 2, it is evident that the most common comorbidity associated with Nephrolithiasis was hypertension (18.88%) followed by Diabetes Meletus (11.93%). 22.32% patients had both Type II Diabetes Meletus and Hypertension. Shang et al.,²⁰ from his study, reported that there is a direct association between urolithiasis and hypertension. It was also revealed that there is increased susceptibility for kidney stones in individuals who are having Hypertension and other conditions related to metabolic syndrome. In another study conducted by Weinberg et al., it was reported that severity of Type 2 diabetes can increase the chances for incidence and recurrence of kidney stone disease. Chung et al.,²¹ from

his study revealed that Nephrolithiasis patients were at increased risk of diabetes after 5 years of follow-up.

Comparison of Risk factors among Case and Control groups

The Figure 1 shows comparison of family history of Nephrolithiasis among the control and test arm and was found that about only 29.38% of the control group had some positive family history of Nephrolithiasis while compared to 70.62% of the test group patients (CI = 95%, p<0.0001) which reveals that it is an being an important predeterminant as non modifiable risk factor for the incidence of Nephrolithiasis.

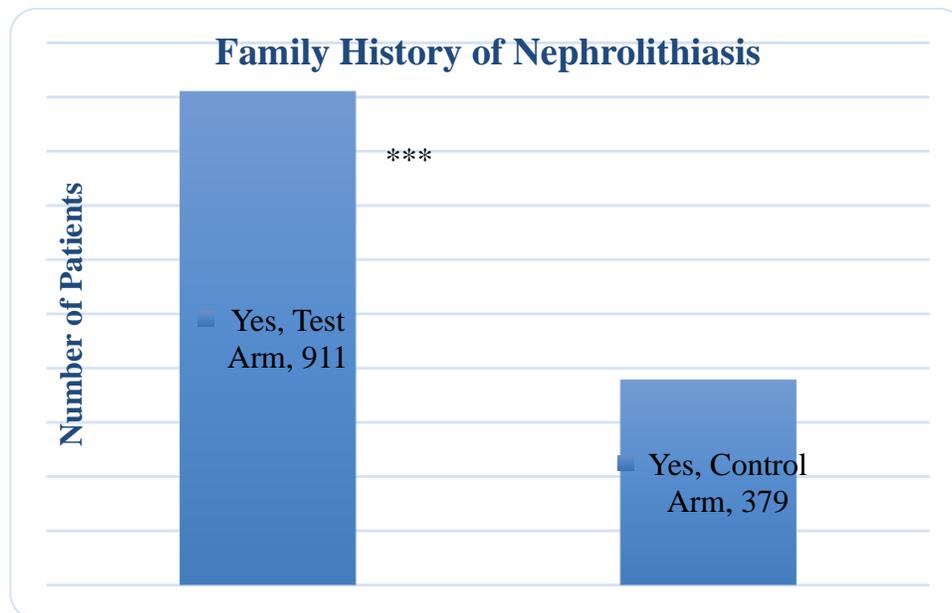


Figure 1: Shows the comparison of family history of Nephrolithiasis among Test and Control group.

Fluid Intake Level	Test Group (N=1290)		Control (N=1290)		P Value
	Number	Percentage	Number	Percentage	
<2L	820	63.54%	419	32.5%	<i>p<0.0001</i>
2-4L	317	24.58%	693	53.64%	
>4L	153	11.87%	178	13.85%	

Table 3: Shows the fluid ingestion among the Study population.

Table 3 compares the amount of fluid ingested in Liter’s by both Control and Test Groups. It was observed that around 63% of patients having nephrolithiasis were taking

less amount of fluid (<2L) when compared to only 32.5% of control group. 24% of the patients in test group were taking 2-4 liters of fluid in a day. The amount of fluid ingested on a daily basis is very crucial in determining the

incidence and recurrence of Urolithiasis as stones are formed in kidney due to the supersaturation of urine. Increasing the intake of fluid has found to be decreasing

the chances of recurrence of future symptomatic painful episodes of nephrolithiasis.

Food Items	Estimated Intake	Nephrolithiasis Patients/Test Group (N=1290)		Control (N=1290)	
		Number	Percentage	Number	Percentage
Tomato	Usually	1010	78.29%	879	68.13%
	Often	231	17.90%	337	26.12%
	Occasionally	49	3.79%	74	5.73%
Spinach	Usually	877	67.98%	702	54.41%
	Often	230	17.82%	270	20.93%
	Occasionally	183	14.18%	318	24.65%
Tea/Coffee	Usually	1237	95.89%	1135	87.98%
	Often	47	3.64%	147	11.39%
	Occasionally	6	0.465%	7	0.54%
Egg	Usually	1173	90.93%	989	76.66%
	Often	69	5.34%	164	12.71%
	Occasionally	48	3.72%	137	10.62%
Colocasia	Usually	876	67.90%	559	43.33%
	Often	173	13.41%	387	30%
	Occasionally	241	18.68%	344	26.66%
Yam	Usually	925	71.70%	684	53.02%
	Often	306	23.72%	298	23.10%
	Occasionally	59	4.57%	308	23.87%
Brinjal	Usually	960	74.41%	808	62.63%
	Often	173	13.41%	240	18.60%
	Occasionally	157	12.17%	242	18.75%
Grapes	Usually	446	34.57%	286	22.17%
	Often	603	46.74%	549	42.55%
	Occasionally	241	18.68%	454	35.19%
Red Meat	Usually	966	74.88%	691	53.56%
	Often	161	12.48%	278	21.55%
	Occasionally	163	12.63%	289	22.4%
Chicken	Usually	923	71.55%	733	56.82%
	Often	215	16.66%	290	22.48%
	Occasionally	152	11.78%	196	15.19%
Sea Food	Usually	1095	84.88%	989	76.66%
	Often	137	10.62%	213	16.51%
	Occasionally	58	4.49%	48	3.72%
Cashew Nut	Usually	483	37.44%	299	23.17%
	Often	424	32.86%	415	32.17%
	Occasionally	383	29.68%	575	44.57%

Table 4: Shows the comparison of dietary risk factors between test and control groups.

Dietary habits are crucial in determining the formation and recurrence of urinary stones, this was compared between the test and control groups shown as in Table 4. The criteria were selected based on the various foods that are rich in stone forming components such as Uric acid and Calcium. The usage of various items was estimated using the keywords, usually for usage more than 3 times in a week or high seasonal usage, often for usage upto 2-3

times in a week and occasionally for use up to 1 time or less in a week.

It was observed that the usage of food substances rich in Uric acid and Calcium were comparatively higher in Test group than the control which may be promoting the increased chances of Nephrolithiasis in the test arm. Mikawlawng et al.,¹⁸ points out that in India, the intestinal hyperabsorption of oxalate is very high due to the

increased dietary oxalate leading to increased urinary oxalate excretion there by increasing the impact of stone formation. Sofia et al.,²³ concluded that in southern India high intake of sodium can cause increased urinary calcium. Giannini S et al.,²⁴ concluded that purines which are predominantly found in animal proteins can act as

precursors of uric acid stones. Vegetables rich in oxalate like tomato, yam, colocasia, spinach and non veg food items rich in purine like red meat, seafood are considered as dietary risk factors of kidney stone. Also, high salt intake can also be a risk factor for stone formation.

Risk Factors		Test Group (N=1290)		Control (N=1290)		Odds Ratio	p Value
		Number	Percentage	Number	Percentage		
Alcohol	Alcoholics	475	36.82%	338	26.20%	1.6416	<i>p</i> <0.0001
	Non-Alcoholics	815	63.17%	952	73.79%		
Cigarette Smoking	Smokers	384	29.76%	299	23.17%	1.40	<i>p</i> =0.0002
	Non-Smokers	906	70.23%	991	76.82%		
Obesity	Obese	776	60.15%	412	31.93%	3.21	<i>p</i> <0.0001
	Non-Obese	514	39.84%	878	68.06%		
Exercise Status	Regularly	551	42.71%	719	55.73%	1.6	<i>p</i> <0.0001
	Rarely	739	57.29%	571	44.26%		

Table 5: Compares the life style risk factors associated with Nephrolithiasis in Test and Control groups

The comparison of risk factors associated with life style disorders among the test and control group is given in Table 5. It reveals that being obese is one of the major risk factors associated with Nephrolithiasis. Analyzing the test group it was observed that 60% of the patients were obese when compared to 31% in control group. The lack of exercise was found also to be contributing to the incidence of kidney stones. Alcoholism was also having a comparable effect in the etiology of Nephrolithiasis. The formation of stones in kidneys can be affected by several life style disorders and dietary factors. Nalini et al.,²⁶ reported that 41.59% patients affected with Nephrolithiasis was prone for Alcohol consumption while 36.03% of the patients were habitual smokers. The high levels of cadmium and lead in the body of smokers may throw some light on the relationship between formation of kidney stones and smoking. There may be a reduction of urinary flow which may increase the concentration of serum cadmium thereby resulting in the induction of Nephrolithiasis. A positive correlation between high BMI and the increased risk of developing renal stones was pointed out by Taylor et al.,⁵ A direct association between obesity and incidence of Urolithiasis in both genders was reported by Nowfar et al.²⁸ Yang Q et al.,³⁰ conducted a study which revealed that kidney injury, its inflammation and fibrosis associated with alcohol ingestion can increase the chances of formation of renal stones. From our study, it was observed that the alcohol consumption and obesity have significant correlation with nephrolithiasis.

CONCLUSION

From all the topics discussed previously, it can be concluded that Nephrolithiasis is a common prevalent condition especially in the Southernmost regions of India. This high incidence can be attributed to the climatic conditions and the eating habits of the population. The chances of recurrence of the condition are also very high even after undergoing proper treatment as most of the patients are not aware about the risk factors that can again provoke the condition. Proper awareness must be created among the patients to bring to their knowledge about the importance in increasing the fluid intake and also to reduce the dietary sources that are rich in minerals that can provoke the type of stone in them.

ACKNOWLEDGEMENT

None

Financial Support

None

REFERENCES

1. Alelign T, Petros B, et.al, kidney disease: An Update on Current Concepts. *Adv Urol.* 2018 Feb 4; 2018:3068365.
2. Coe F. L., Evan A., Worcester E, et.al, Kidney stone disease. *Journal of Clinical Investigation.* 2005;115(10):2598–2608.
3. Barbasa C., Garciaa A., Saavedra L., Muros M, et.al, Urinary analysis of nephrolithiasis markers. *Journal of Chromatography B.* 2002;781(1-2):433–455.
4. Patrick Jones, MRCS,1 Sadaf Karim Sulaiman, MRCS,1 Kithmini N. Gamage, MBChB,1 TheodorasTokas, MD, PhD, FEBU,2 EnaksheeJamnadass, MBChB,1 et.al, Do Lifestyle Factors Including Smoking, Alcohol, and

- Exercise Impact Your Risk of Developing Kidney Stone Disease? Outcomes of a Systematic Review, *Journal Of Endourology*, January 2021, Volume 35, Pg no:1–7.
5. Rule, Andrew D, Krambeck, Amy E, Lieske, John C, et.al, Chronic Kidney Disease in Kidney Stone Formers. *Clinical Journal of the American Society of Nephrology*, August 2011. 6(8):p 2069-2075,
 6. Chuang, TF., Hung, HC., Li, SF. et al. Risk of chronic kidney disease in patients with kidney stones—a nationwide cohort study. *BMC Nephrology*, (2020), 21, 292 .
 7. Rule AD, Bergstralh EJ, Melton LJ 3rd, Li X, Weaver AL, Lieske JC, et.al, Kidney stones and the risk for chronic kidney disease. *Clin J Am Soc Nephrol*. 2009 Apr;4(4):804-11.
 8. Gambaro G., Fabris A., Puliatta D., Lupo A, et.al, Lithiasis in cystic kidney disease and malformations of the urinary tract. *Urological Research*. 2006;34(2):102–107
 9. Moryama M. T., Domiki C., Miyazawa K., Tanaka T., Suzuki K, et.al, Effects of oxalate exposure on Madin-Darby canine kidney cells in culture: renal prothrombin fragment-1 mRNA expression. *Urological Research*. 2005;33(6):470–475.
 10. Kumar S., Sigmon D., Miller T., et al. A new model of nephrolithiasis involving tubular dysfunction injury. *Journal of Urology*. 1991;146(5):1384–1389.
 11. Lieske JC, Rule AD, Krambeck AE, Williams JC, Bergstralh EJ, Mehta RA, Moyer TP, et.al, Stone composition as a function of age and sex. *Clin J Am Soc Nephrol*. 2014 Dec 5;9(12):2141-6.
 12. Cetin N, Gencler A, KavazTufan A. et.al, Risk factors for development of urinary tract infection in children with nephrolithiasis. *J Paediatr Child Health*. 2020 Jan;56(1):76-80.
 13. Johnson RJ, Perez-Pozo SE, Lillo JL, Grases F, Schold JD, Kuwabara M, Sato Y, Hernando AA, Garcia G, Jensen T, Rivard C, Sanchez-Lozada LG, Roncal C, Lanaspá MA et.al., Fructose increases risk for kidney stones: potential role in metabolic syndrome and heat stress. *BMC Nephrol*. 2018 Nov 8;19(1):315.
 14. Yang J, Sun H, Wan S, Mamtawla G, Gao X, Zhang L, Li Y, Wang X, Li J et.al, Risk Factors for Nephrolithiasis in Adults with Short Bowel Syndrome. *Ann NutrMetab*. 2019;75(1):47-54.
 15. Tangren JS, Powe CE, Ecker J, Bramham K, Ankers E, Karumanchi SA, Thadhani R. et.al, Metabolic and Hypertensive Complications of Pregnancy in Women with Nephrolithiasis. *Clin J Am SocNephrol*. 2018 Apr 6;13(4):612-619.
 16. Khan SR, Glenton PA, Backov R, Talham DR.et.al, Presence of lipids in urine, crystals and stones: implications for the formation of kidney stones. *Kidney Int*. 2002 Dec;62(6):2062-72.
 17. Knoll T, et.al, Epidemiology, pathogenesis and pathophysiology of urolithiasis. *European Urology Supplements*. 2010;9(12):802–806.
 18. Mikawlawng K, Kumar S, Vandana R, et al. Current scenario of urolithiasis and the use of medicinal plants as antiurolithiatic agents in Manipur (North East India): a review. *International Journal of herbal medicine*. 2014;2(1):1-2
 19. Morton AR, Iliescu EA, Wilson JW, et al. Nephrology: 1. Investigation and treatment of recurrent kidney stones. *CMAJ*. 2002 Jan 22;166(2):213-8
 20. Sha Shang W, Li Y, Ren Y, Yang Y, Li H, Dong J, et.al, Nephrolithiasis and risk of hypertension: a meta-analysis of observational studies. *BMC Nephrol*. 2017 Nov 29;18(1):344.
 21. Chung EN, Stampfer MJ, Curhan GC, et al. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol*. 2004 Dec;15(12):3225-32.
 22. Yuan K, Larsson SC, et al. Assessing causal associations of obesity and diabetes with kidney stones using Mendelian randomization analysis. *Mol Genet Metab*. 2021 Sep-Oct;134(1-2):212-215.
 23. Reddy ST, Wang CY, Sakhaee K, Brinkley L, Pak CY, et al. Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism. *Am J Kidney Dis*. 2002 Aug;40(2):265-74
 24. Kourambas, J et al. “Role of stone analysis in metabolic evaluation and medical treatment of nephrolithiasis.” *Journal of endourology* vol. 15,2 (2001): 181-6.
 25. Ferraro, Pietro Manuel et al. “Dietary and Lifestyle Risk Factors Associated with Incident Kidney Stones in Men and Women.” *The Journal of urology* vol. 198,4 (2017): 858-863.
 26. Guha, Manalee et al. “The Demographic Diversity of Food Intake and Prevalence of Kidney Stone Diseases in the Indian Continent.” *Foods (Basel, Switzerland)* vol. 8, 1 37. 21 Jan. 2019.
 27. Cetin, Nuran et al. “Risk factors for development of urinary tract infection in children with nephrolithiasis.” *Journal of paediatrics and child health*, 2020, vol. 56 (1), 76-80.
 28. Pietro Manuel Ferraro and Matteo Bargagli, et.al, Dietetic and lifestyle accommodations for stone formers, monographic: urinary stone disease medical treatment *Urol*. 2021; vol. 74 (1): 112-122
 29. Brain E, Geraghty RM, Cook P, Roderick P, Somani B, et.al, Risk of UTI in kidney stone formers: a matched-cohort study over a median follow-up of 19 years. *World J Urol*. 2021 Aug; vol. 39(8):3095-3101.
 30. Yang Q, Chen HY, Wang JN, Han HQ, Jiang L, Wu WF, et al. Alcohol promotes renal fibrosis by activating Nox2/4-mediated DNA methylation of Smad7. *Clin Sci (Lond)*. 2020 Jan 31;134(2):103-122.