ENHANCED FORMULA

The new approach
to the maintenance
of proper renal function

Renal N

WITH THE EXCLUSIVE LIVE STRAIN OF LACTOBACILLUS ACIDOPHILUS

NEW

WITH IMMUNOFOS®

Candioli PHARMA

www.candioli.com

THE GUT-KIDNEY AXIS:

A NEW STRATEGY FOR THE MANAGEMENT OF CHRONIC KIDNEY DISEASE

MICROBIOTA AND PROPER INTESTINAL FUNCTION:

Deep qualitative-quantitative changes in intestinal microflora (dysbiosis) occur starting from the earliest stages of CKD [1,4,6,7,24,25,30,31,32]

Altered digestive metabolism, changes in endoluminal pH, alterations in mucosal permeability, accumulation of inflammatory cytokines leading to:[4,6,7,15,23,24,27,28,31,32]

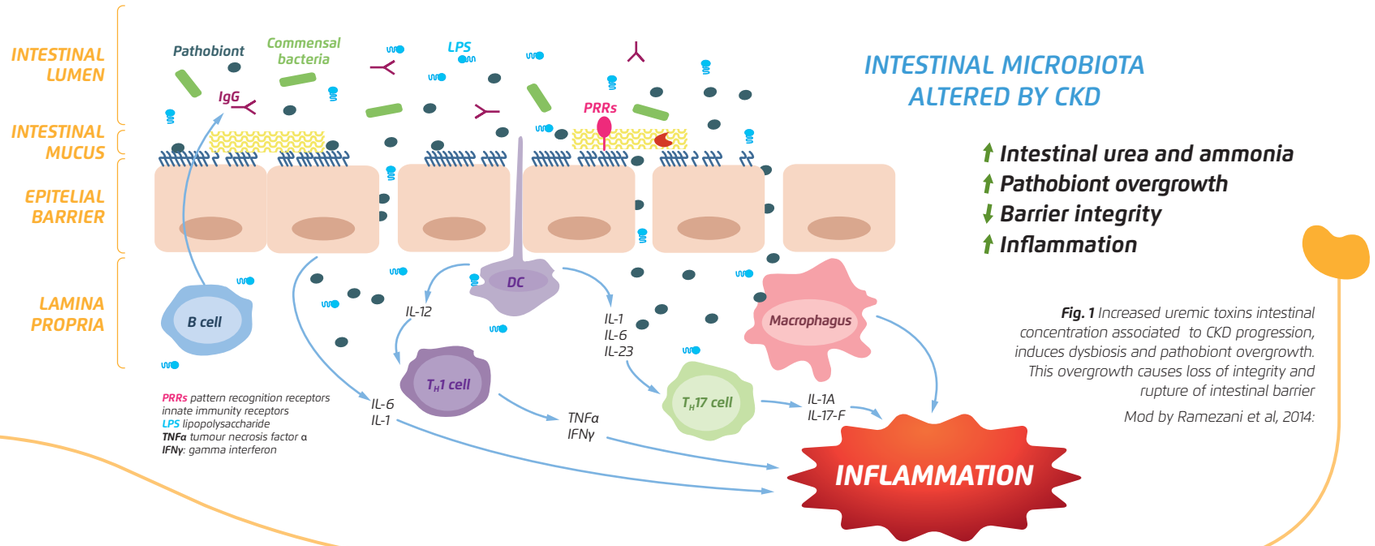


Fig. 1 *Increased uremic toxins intestinal concentration associated to CKD progression, induces dysbiosis and pathobiont overgrowth. This overgrowth causes loss of integrity and rupture of intestinal barrier*

Mod by Ramezani et al, 2014:

NITROGEN TOXIN ACCUMULATION

produced in the intestine and subsequent systemic absorption (phenols, indoxyl sulphate, cresols, amines and polyamines, phenylacetic acid, ammonia, etc.)[1,4,6,7,9,16,17]

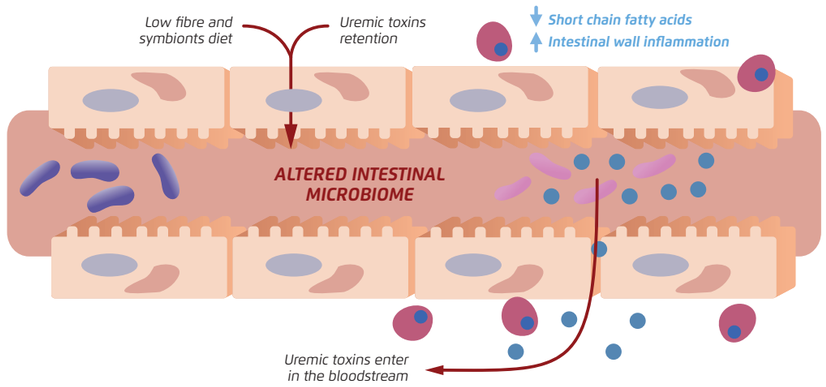


Fig. 2 *Intestinal uremic toxins retention, including urea, alters microbial population*

From Lau EWL, et al 2018.

CKD PROGRESSION [4,16,17,24,27,28]

CARDIOVASCULAR COMPLICATIONS [16,17,18,27,28]

ANEMIA [16,17,30,31]

LOCAL AND SYSTEMIC OXIDATIVE DAMAGE [2,6,7,23,24,25,31,32]

ALTERED CALCIUM-PHOSPHORUS METABOLISM [16,17,24]

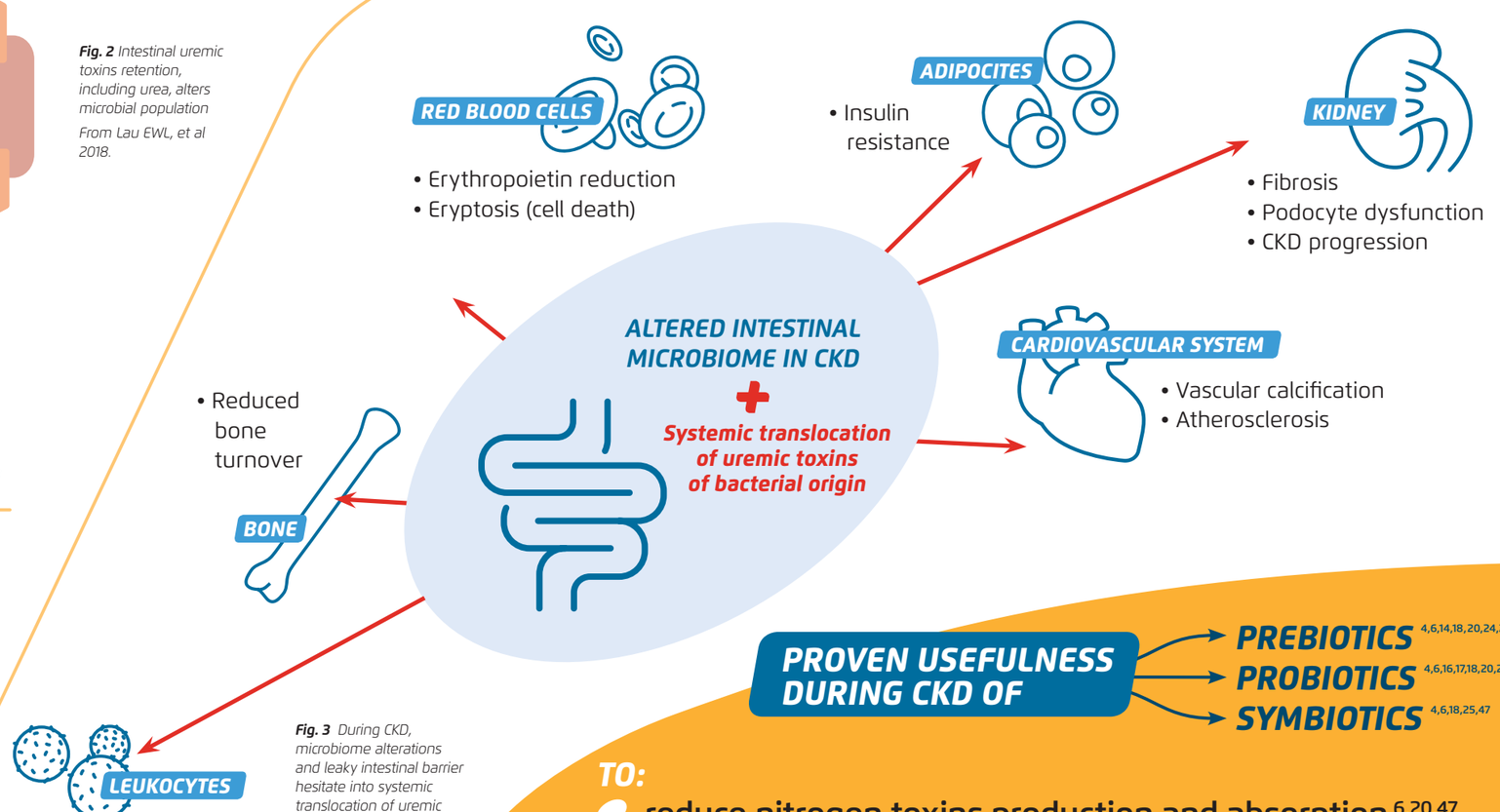


Fig. 3 *During CKD, microbiome alterations and leaky intestinal barrier hesitate into systemic translocation of uremic toxins of bacterial origin such as indoxyl-sulphate and p-cresyl-sulphate*

From Lau et al, 2018.

PROVEN USEFULNESS DURING CKD OF

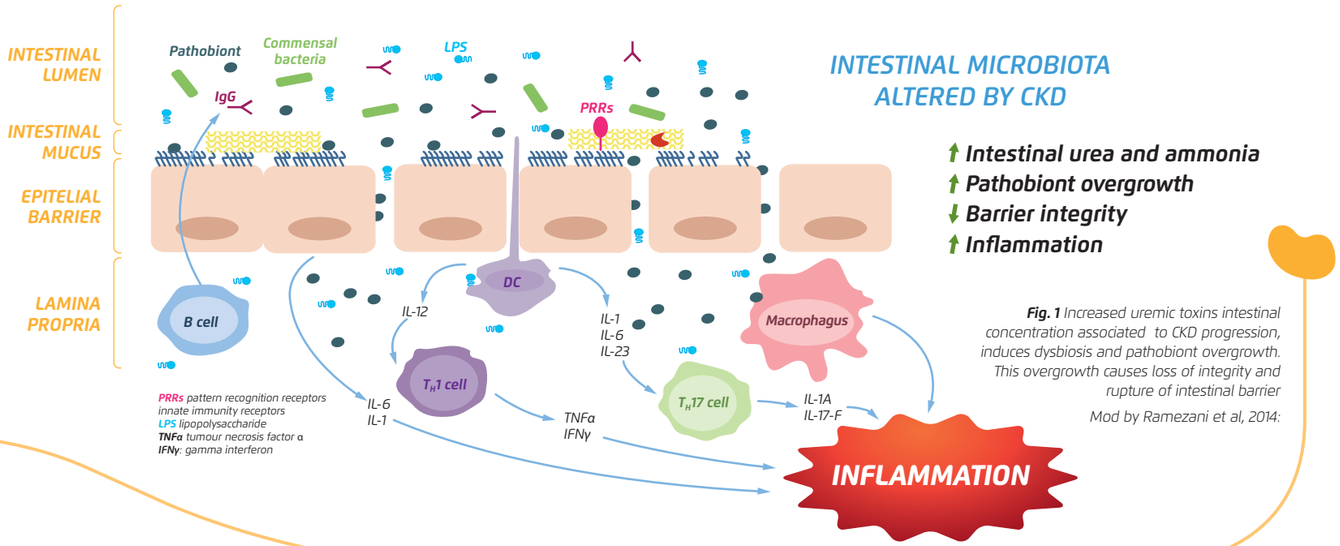
- **PREBIOTICS** [4,6,14,18,20,24,25,31,32,35,36,38,47]
- **PROBIOTICS** [4,6,16,17,18,20,24,25,30,32,35,38,47]
- **SYMBIOTICS** [4,6,18,25,47]

TO:

- reduce nitrogen toxins production and absorption [6,20,47]
- modulate inflammation and immunity [19,20]
- preserve residual renal function [6,15,16,17]

THE GUT-KIDNEY AXIS:

A NEW STRATEGY FOR THE MANAGEMENT OF CHRONIC KIDNEY DISEASE

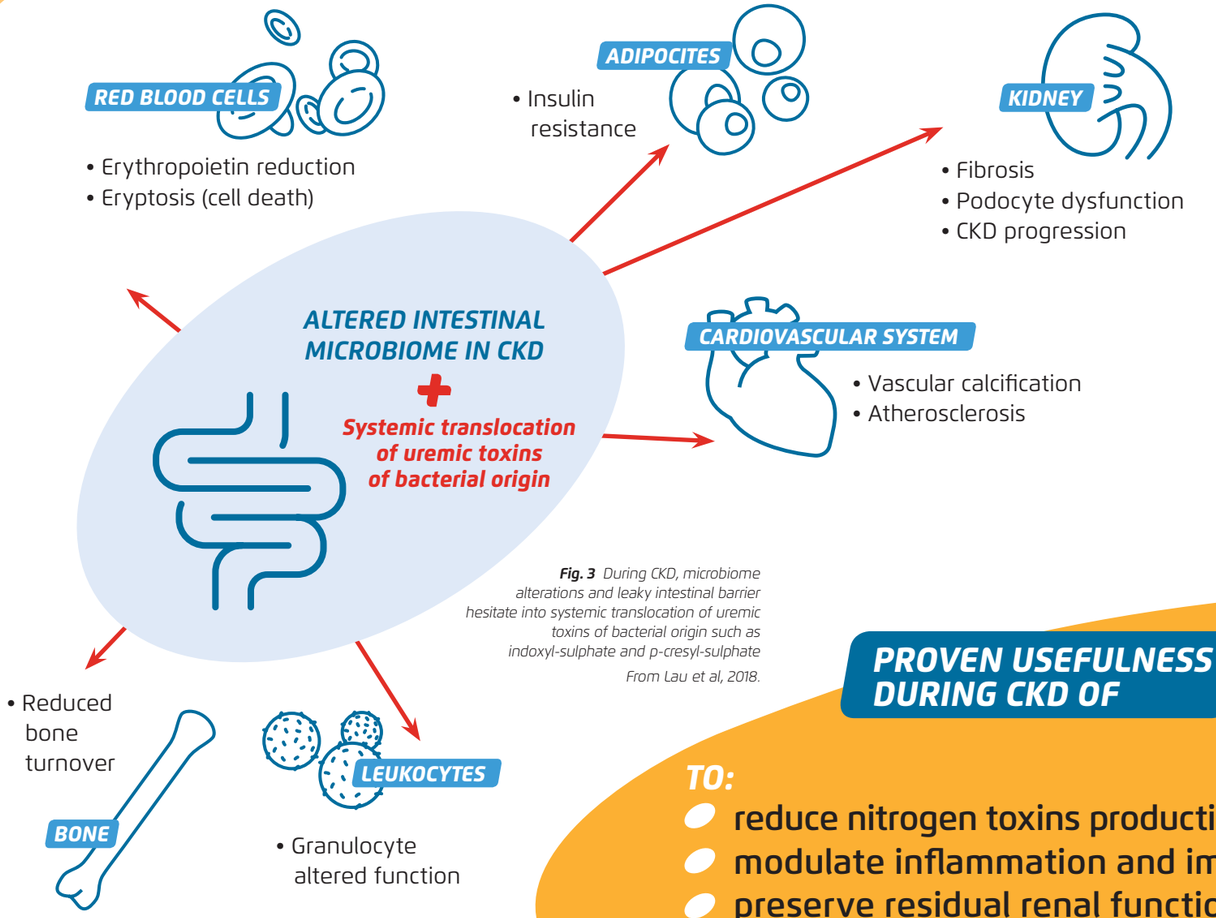


INTESTINAL MICROBIOTA ALTERED BY CKD

- ↑ Intestinal urea and ammonia
- ↑ Pathobiont overgrowth
- ↓ Barrier integrity
- ↑ Inflammation

Fig. 1 *Increased uremic toxins intestinal concentration associated to CKD progression, induces dysbiosis and pathobiont overgrowth. This overgrowth causes loss of integrity and rupture of intestinal barrier*

Mod by Ramezani et al, 2014:



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ENHANCED FORMULA

THE EXCLUSIVE LIVE STRAIN OF LACTOBACILLUS ACIDOPHILUS (CECT 4529)

(AUTHORISED BY EFSA IN ACCORDANCE WITH REGULATION (EC) NO 2018/1558)

AUTHORISED AS GUT FLORA STABILISER FOR DOGS AND CATS[8]

Lactobacillus acidophilus, one of the most studied probiotics for its effects on intestinal well-being of dogs and cats[2,8,10,40,44,48,49]

- An imbalance of the intestinal microflora (dysbiosis) induces an **increased toxic nitrogen wastes derived from** protein catabolism[15,16,17,20,24,30,31,32,38,46,47]
- L. acidophilus is one of the **most active** probiotic strains in reducing nitrogenous toxins production[6,24,31,32,47,48]
- Digestive processes optimisation, induced by simultaneous administration of scFOS[26,40] and L. acidophilus **reduces digestive symptoms** that characterize CKD (vomiting, diarrhoea, dysorexia) and **significantly reduces nitrogen toxins production**[15,18,20,24,31,32,38,40,47]
- Reduced nitrogenous toxins absorption of intestinal origin[15,16,17,18,24,47] **induces positive local effects** (nephroprotection, slower progression of CKD) and systemic effects[23,24,31,32,47]

SCFOS PROFEED®

They modify activity and composition of intestinal microflora (promoting bifidobacteria and lactobacilli growth and reducing the presence of pathogenic bacteria)[10,40]

They limit toxins synthesis originating from protein metabolism (ammonia, aliphatic amines, indoles, phenols and sulphur compounds)[7,14,18,20,24,40]

NEW

ImmunoFOS®

FERMENTED OF FOS BY LACTOBACILLUS PARACASEI CNCM STRAIN I-5220

Postbiotics are an **innovative class of molecules (peptides)** naturally derived from microbial fermentation that:

- **contribute** to the microbiota balance[39,41,42]
- **control** local inflammation[39,41,42]
- **improve** intestinal epithelial barrier integrity[33,39,41,42]
- **reduce** bacterial translocation risk and absorption of pro-inflammatory metabolites[39,50]

OLIVE OIL POLYPHENOLS

EFFECTS ON KYDNEYS

- **ANTIHYPERTENSIVE** [21,34,37,45]
- **ANTIOXIDANTS** [12,29,34,37]
- **ANTI-INFLAMMATORY** [29,34,37]
- **NEPHROPROTECTIVE** [12]

Hypotensive and vasodilator effects of olive oil polyphenols are useful in case of experimentally induced renal dysfunction because **they increase GFR**[21,22] (glomerular filtration rate) and **reduce creatinine plasma concentration**[21,22]

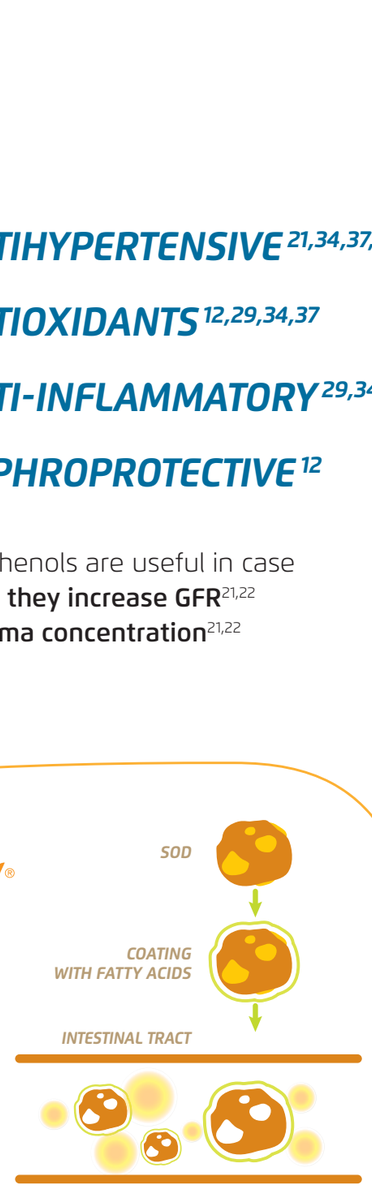
NEW

MELOFEED®

melofeed®

Melofeed® raw material from melon containing SOD

SOD is one of the main antioxidant defensive systems active at renal level[3,13,43].
During CKD, there is an increase of free radicals production[3,13,43], and consequently of systemic blood pressure[3]



Progressive release of SOD

GROUP B VITAMINS

STIMULATE HEMATOPOIESIS[11]

Group B vitamins (Vit. B12, Vit. B6 and folic acid) are important nutritional factors in haemoglobin and red blood cells[11] synthesis. **They help control chronic non-regenerative anemia resulting from CKD.**

Renal N

Contains Lactobacillus acidophilus, Olea Europaea and Fructoligosaccharides

COMPOSITION

Renal N powder Maltodextrin, Fructooligosaccharides 30%, Fermented Fructooligosaccharides (*ImmunoFOS), Sodium pyrophosphate, Yeasts [brewer's yeast], Lupine protein flour, Products obtained from vegetable processing (Melon) (*Melofeed), Vegetable oils and fats (Sunflower oil)
Renal N palatable paste Fructoligosaccharides 25%, Vegetable oils and fats (Soya oil, Sunflower oil), Fermented fructoligosaccharides (*ImmunoFOS), Malt (Extract), Glycerol monostearate, Products obtained from vegetable processing (Melon) (*Melofeed), Maltodextrin

ADDITIVES PER KG

Renal N powder *Vitamins:* Vitamin E 3a700 IU 25,000 - Vitamin B6 3a831 mg 10,000 - Folic acid 3a316 mg 4,000 - Vitamin B12 mg 100 *Stabilizers of the intestinal flora:* Lactobacillus acidophilus CECT 4529 4b1715 UFC 6,3x10[11] *Anti-caking agents:* Colloidal silica E551b mg 25,000 *Organoleptic additives:* Olea europaea L.: Olive extract mg 20.000
Renal N palatable paste *Vitamins:* Vitamin E 3a700 IU 25,000 - Vitamin B6 3a831 mg 10,000 - Folic acid 3a316 mg 4,000 - Vitamin B12 mg 100 *Stabilisers of the intestinal flora:* Lactobacillus acidophilus CECT 4529 4b1715 UFC 6,3x10[11] *Organoleptic additives:* Olea europaea L.: Olive extract mg 20.000

INSTRUCTIONS FOR PROPER USE

Renal N powder Mix with the usual food ration at a rate of 0.2 g of powder per kg of body weight per day, corresponding to the daily quantities indicated in the table. It is possible to divide the daily quantity into 2-3 rations, based on the number of main meals, in 30-day cycles.

Powder per day

1 small scoop level	every 2,5 kg of b.w.	**1 big scoop level**	every 10 kg of b.w.

Renal N palatable paste Administer directly into the mouth or mix with the usual food ration in proportion to the daily quantities indicated in the table. Administer **Renal N** palatable paste in cycles of 30 days. Fresh water at will is recommended.

Paste per day

Cats	1 ml for every 5 kg of b.w.	**Dogs 0-10 kg**	1 ml for every 5 kg of b.w.

Renal N is a complementary feed for dogs and cats

Bibliography

1. **Barrios C, et al.** Gut-microbiota-metabolite axis in early renal function decline. *PLoS ONE 10(8): e0134311. doi:10.1371/journal.pone.0134311*
2. **Bigliati M, et al.** Lactobacillus acidophilus as a probiotic in healthy adult cats. *Poster presented at SISVET1 Congress 2018. Turin*
3. **Brown SA.** Oxidative stress and chronic kidney disease. *Vet Clin Small Anim 2008;38:157-166*
4. **Castillo-Rodriguez E, et al.** Impact of altered intestinal microbiota on chronic kidney disease progression. *Toxins 2018;10:300*
5. **Chung S, et al.** Oleanolic acid attenuates renal fibrosis in mice with unilateral obstruction via facilitating nuclear translocation of Nrf2. *Nutrition and Metabolism 2014;11:2*
6. **Cigarran Guldris S, et al.** Gut microbiota and chronic kidney disease. *Nefrologia 2017;37(1):9-19*
7. **Di Iorio BR, et al.** Urea and impairment of the gut-kidney axis in chronic kidney disease. *G Ital Nefrol 2017;ISSN 1724-5990*
8. **EFSA.** Safety and efficacy of Lactobacillus acidophilus D2/CSL (Lactobacillus acidophilus CECT 4529) as a feed additive for cats and dogs. *EFSA Journal 2018;16(5):5278*
9. **Friedman EA.** Can the bowel substitute for the kidney in advanced renal failure? *Current Medical Research and Opinions 2009;25(8):1913-1918*
10. **Gagnè JW, et al.** Effects of a synbiotic on fecal quality, short chain fatty acids concentrations and the microbiome of healthy sled dogs. *BMC Veterinary Research 2013;9:246*
11. **Hand MS, et al.** Small Animal Clinical Nutrition. *5th edition 2010. Mark Morris Institute ed.*
12. **Hong YA, et al.** Delayed treatment with oleanolic acid attenuates tubulointerstitial fibrosis in chronic cyclosporine nephropathy throughNrf2/HO-1 signaling. *Journal of Translational Medicine 2014;12:50*
13. **Keegan RF, et al.** Oxidative stress and neutrophil function in cats with chronic renal failure. *J Vet Intern Med 2010;24:514-519*
14. **Kieffer DA, et al.** Impact of dietary fibers on nutrient management and detoxification organs:gut, liver and kidneys. *Adv Nutr 2016;7:1111-1121*
15. **Koppe L, et al.** The role of gut microbiota and diet on uremic retention solutes production in the context of chronic kidney disease. *Toxins 2018;10:155*
16. **Lau WL, et al.** Altered microbiome in chronic kidney disease:systemic effects of gut-derived uremic toxins. *Clinical Science 2018;132:509-522*
17. **Lau WL, et al.** The leaky gut and altered microbiome in chronic kidney disease. *Journal of Renal Nutrition 2017;27(6):458-461*
18. **Lekawanvijit S.** Role of gut-derived protein-bound uremic toxins in cardiorenal syndrome and potential treatment modalities. *Circ J 2015;79:2088-2097*
19. **Levy M, et al.** Microbiome, metabolites, and host immunity. *Current Opinion in Microbiology 2017;35:8-15*
20. **Lopes RCSO, et al.** Modulation of intestinal microbiota, control of nitrogen products and inflammation by pre/probiotics in chronic kidney disease: a systematic review. *Nutr Hosp 2018;35:722-730*
21. **Madlala HP, et al.** Changes in renal function and oxidative status associated with the hypotensive effects of oleanolic acid and related synthetic derivatives in experimental animals. *PLoS ONE 10(6): e0128192. Doi10.1371/journal.pone.0128192*
22. **Mapanga RF, et al.** Renal effects of plant-derived oleanolic acid in streptozocin-inducet diabetic rats. *Renal Failure 2009;31:481-491*
23. **Meijers B, et al.** Intestinal barrier function in chronic kidney disease. *Toxins 2018;10:298; doi:10.3390/toxins10070298*
24. **Nallu A, et al.** Gut microbiome in CKD: challenges and opportunity. *Transl Res 2017;179:24-37*
25. **Pisano A, et al.** Biotic supplements for renal patients: a systematic review and meta-analysis. *Nutrients 2018;10:1224; doi:10.3390/nu10091224*
26. **Pluznik JL.** Gut microbiota in renal physiology: focus on short-chain fatty acids and their receptors. *Kidney Int 2016;90(6):1191-1198*
27. **Poesen R, et al.** Renal clearance and intestinal generation of p-cresyl sulfate and indoxyl sulfate in CKD. *Clin J Am Soc Nephrol 2013;8:1508-1514*
28. **Poesen R, et al.** The influence of dietary protein intake on mammalian tryptophan and phenolic metabolites. *PLOS ONE | DOI:10.1371/journal.pone.0140820 October 15, 2015*
29. **Pollier J.** Oleanolic acid. *Phytochemistry 2012;77:10-15*
30. **Prokopienko AJ, et al.** Microbiota-derived uremic retention solutes: perpetrators of altered nonrenal drug clearance in kidney disease. *Expert Rev Clin Pharmacol 2018;11(1):71-82*
31. **Ramezani A, et al.** The gut microbiome, kidney disease and targeted interventions. *J Am Soc Nephrol 2014;25:657-670*
32. **Ramezani A, et al.** Role of the gut microbiome in uremia: a potential therapeutic target. *Am J Kidney Dis 2016;67(3):483-498*
33. **Rescigno M.** Intestinal microbiota and its effect on the immune system. *Cellular Microbiology 2014;16(7):1004-1013*
34. **Rodriguez-Rodriguez R.** Oleanolic acid and related triterpenoids from olives on vascular function: molecular mechanisms and therapeutic perspectives. *Current Medicinal Chemistry 2015;22:1414-1425*
35. **Rossi M, et al.** Pre-, pro-, and synbiotics: do they have a role in reducing uremic toxins? A systematic review and meta-analysis. *Int J Nephrol 2012; doi:10.1155/2012/673631*
36. **Rossi M, et al.** Synbiotics easing renal failure by improving gut microbiology (SYNERGY): a randomized trial. *Clin J Am Soc Nephrol 2016;11:223-231*
37. **Sanchez-Quesada C, et al.** Bioactive properties of the main triterpenes found in olives, virgin olive oil and leaves of Olea europaea. *J Agric Food Chem 2013;61:2173-12182*
38. **Schepers E, et al.** The gut: the forgotten organ in uremia? *Blood Purif 2010;29:130-136*
39. **Spadoni I, et al.** A gut-vascular barrier controls the systemic dissemination of bacteria. *Science 2015;350:6262*
40. **Swanson KS, et al.** Fructooligosaccharides and Lactobacillus acidophilus modify gut microbial populations, total tract nutrient digestibility and fecal protein catabolite concentrations in healthy adult dogs. *J Nutr 2002;132:3721-3731*
41. **Tsilingiri K, et al.** Postbiotics: what else? *Beneficial Microbes 2013;4(1):101-107*
42. **Tsilingiri K, et al.** Probiotic and postbiotic activity in health and disease: comparison of a novel polarised ex-vivo organ culture model. *Gut (2012). doi:10.1136/gutjnl-2011-300971*
43. **Tylicky L, et al.** Antioxidants: a possible role in kidney protection. *Kidney Blood Press Res 2003;26:303-314*
44. **Tzortzis G, et al.** Modulation of antipathogenic activity in canine-derived Lactobacillus species by carbohydrate growth substrate. *J Appl Microbiol 2004;96:552-559*
45. **Valero-Munoz M, et al.** Protective effect of a pomace olive oil concentrated in triterpenic acids in alterations related to hypertension in rats: mechanisms involved. *Mol Nutr Food Res 2014;58:376-383*
46. **Vanholder R, et al.** Pathophysiologic effects of uremic retention solutes. *J Am Soc Nephrol 1999;10:1815-1823*
47. **Vanholder R, et al.** The intestine and the kidneys: a bad marriage can be hazardous. *Clin Kidney J 2015;0:1-12*
48. **Vemuri R, et al.** Lactobacillus acidophilus DDS-1 modulates the gut microbiota and improves metabolic profile in aging mice. *Nutrients 2018;10:1255*
49. **Wynn SG.** Probiotics in veterinary practice. *JAVMA 2009;234(5):606-613*
50. **Zagato E, et al.** L. paracasei CBA L74 meetabolic products and fermented milk for infant formula have anti-inflammatory activity on dendritic cells in vitro and protective effects against colitis and an enteric pathogen in vivo. *PlosOne 2014;9(2); doi:10.1371/journal.pone.0087615*

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