Klotho: The Super-Antioxidant You've Never Heard of

Jenna Henderson, ND

Complete References

1. Sosnowski B, et al. [Klotho not only antiageing protein]. *Przegl Lek.* 2017;74(1):25-9.

2. Kuro-o M. Klotho and aging. *Biochim Biophys Acta.* 2009 Oct;1790(10):1049-58.

3. Zhou X, et al. Tetrahydroxystilbene glucoside extends mouse life span via upregulating neural klotho and downregulating neural insulin or insulin-like growth factor 1. *Neurobiol Aging.* 2015 Mar;36(3):1462-70.

4. Kale A, et al. Klotho in kidney diseases: A crosstalk between the renin-angiotensin system and endoplasmic reticulum stress. *Nephrol Dial Transplant.* 2021 Nov 26;gfab340.

5. Mochón-Benguigui S, et al. Is Sleep Associated with the S-Klotho Anti-Aging Protein in Sedentary Middle-Aged Adults? The FIT-AGEING Study. *Antioxidants (Basel).* 2020 Aug 12;9(8):738.

6. Pákó J, et al. *Decreased Levels of Anti-Aging Klotho in Obstructive Sleep Apnea.* 2020 Jun;23(3):256-261.

7. Mohanty S, Suchiang K. Triiodothyronine (T3) enhances lifespan and protects against oxidative stress via activation of Klotho in Caenorhabditis elegans. *Biogerontology.* 2021 Aug;22(4):397-413.

8. Dote-Montero M, et al. Predictors of Sexual Desire and Sexual Function in Sedentary Middle-Aged Adults: The Role of Lean Mass Index and S-Klotho Plasma Levels. The FIT-AGEING Study. *J Sex Med.* 2020 Apr;17(4):665-677.

9. Abraham C, et al. Klotho Is a Neuroprotective and Cognition-Enhancing Protein. *Vitam Horm.* 2016;101:215-38.

10. Dubal D, et al. Life extension factor klotho enhances cognition. *Cell Resp.* 2014 May 22;7(4):1065-76.

11. Zhao Y, et al. Klotho overexpression improves amyloid-β clearance and cognition in the APP/PS1 mouse model of Alzheimer's disease. *Aging Cell.* 2020 Sep 21;19(10):e13239.

12. Sanz B, et al. Low serum klotho concentration is associated with worse cognition, psychological components of frailty, dependence, and falls in nursing home residents. *Sci Rep.* 2021 Apr 27;11(1):9098.

13. Benoit B, et al. Fibroblast growth factor 19 regulates skeletal muscle mass and ameliorates muscle wasting in mice. *Nat Med.* 2017 Aug;23(8):990-996.

14. Semba R, et al. Relationship of low plasma klotho with poor grip strength in older community-dwelling adults: the InCHIANTI study. *Eur J Appl Physiol.* 2012 Apr;112(4):1215-20.

15. Cheng Y, et al. Association between Soluble α-Klotho Protein and Metabolic Syndrome in the Adult Population. *Biomolecules.* 2022 Jan 4;12(1):70.

16. Rao Z, et al. Administration of alpha klotho reduces liver and adipose lipid accumulation in obese mice. *Heliyon.* 2019 Apr 24;5(4):e01494.

Klotho – The Super Antioxidant You've Never Heard Of

References

17. Isakova T, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int.* 2011 Jun;79(12):1370-8.
18. Chen G, et al. α-Klotho is a non-enzymatic molecular scaffold for FGF23 hormone signalling. *Nature.* 2018 Jan 25;553(7689):461-466.
19. Razzaque M. The FGF23-Klotho axis: endocrine regulation of phosphate homeostasis. *Nat Rev Endocrinol.* 2009 Nov;5(11):611-9.
20. Kuro-o M. Klotho. *Pflugers Arch.* 2010 Jan;459(2):333-43.
21. Olauson H, Larsson T. FGF23 and Klotho in chronic kidney disease. *Curr Opin Nephrol Hypertens.* 2013 Jul;22(4):397-404.
22. Mituła I, et al. [FGF-23 and Klotho protein - new markers in chronic kidney disease?]. *Pol Merkur Lekarski.* 2013 Apr;34(202):235-8.
23. Kendrick J, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol.* 2011 Oct;22(10):1913-22.
24. Silver J, Naveh-Many T. FGF-23 and secondary hyperparathyroidism in chronic kidney disease. *Nat Rev Nephrol.* 2013 Nov;9(11):641-9.
25. Xing L, et al. Klotho ameliorates diabetic nephropathy by activating Nrf2 signaling pathway in podocytes. *Biochem Biophys Res Commun.* 2021 Jan 1;534:450-456.
26. Zubkiewicz-Kucharska A, Wikiera B, Noczyńska A. Soluble Klotho Is Decreased in Children With Type 1 Diabetes and Correlated With Metabolic Control. Front Endocrinol (Lausanne). 2021 Sep17;12:709564.
27. Bergmark B, et al. Klotho, fibroblast growth factor-23, and the renin-angiotensin system - an analysis from the PEACE trial. *Eur J Heart Fail.* 2019 Apr;21(4):462-470.
28. Zhou X, et al. Klotho gene deficiency causes salt-sensitive hypertension via monocyte chemotactic protein-1/CC chemokine receptor 2-mediated inflammation. J Am Soc Nephrol. 2015 Jan;26(1):121-32.
29. Kawarazaki W, et al. Salt causes aging-associated hypertension via vascular Wnt5a under Klotho deficiency. *J Clin Invest.* 2020 Aug 3;130(8):4152-4166.
30. Sari F, et al. High serum soluble α-Klotho levels in patients with autosomal dominant polycystic kidney disease. *J Investing Med.* 2017 Feb;65(2):358-362.
31. Martín-González C, et al. Alpha-Klotho protein in systemic lupus erythematosus. *Clin Exp Rheumatol.* 2022 Mar 11.
32. Ye H, et al. microRNA-199a may be involved in the pathogenesis of lupus nephritis via modulating the activation of NF-κB by targeting Klotho. *Mol Immunol.* 2018 Nov;103:235-242.
33. Takenaka T, et al. Klotho supplementation attenuates blood pressure and albuminuria in murine model of IgA nephropathy. *J Hypertens.* 2021 Aug 1;39(8):1567-1576.
34. Maeda A, et al. The Role of Extracellular Phosphate Levels on Kidney Disease Progression in a Podocyte Injury Mouse Model. *Nephron.* 2019;142(2):135-146.
35. Kim J, et al. Klotho plays a critical role in clear cell renal cell carcinoma progression and clinical outcome. *Korean J Physiol Pharmacol.* 2016 May;20(3):297-304.
36. Zhang A, et al. Relationship of Serum Soluble Klotho Levels and Echocardiographic Parameters in Patients on Maintenance Hemodialysis. *Kidney Blood Press Res.* 2019;44(3):396-404.
37. Yang K, et al. Amelioration of uremic toxin indoxyl sulfate-induced endothelial cell dysfunction by Klotho protein. *Toxicol Lett.* 2012 Nov 30;215(2):77-83.
38. Kim S, et al. Klotho as a potential predictor of deceased donor kidney transplantation outcomes. *Ann Surg Treat Res.* 2020 Jun;98(6):332-339.

References

39. Liu Y, et al. Positive correlation of serum fibroblast growth factor 23 with peripheral arterial stiffness in kidney transplantation patients. *Clin Chim Acta.* 2020 Jun;505:9-14.
40. Navarro-García J, et al. Fibroblast Growth Factor-23-Klotho Axis in Cardiorenal Syndrome: Mediators and Potential Therapeutic Targets. *Front Physiol.* 2021 Nov 15;12:775029.
41. Klotho Therapeutics Website. Applications of Klotho Human Protein. Available at: https://www.klotho.com/. Accessed April 3, 2022.
42. Franco M, Beyerstedt S, Rangel E. Klotho and Mesenchymal Stem Cells: A Review on Cell and Gene Therapy for Chronic Kidney Disease and Acute Kidney Disease. *Pharmaceutics.* 2021 Dec 21;14(1):11.
43. Tang C, et al. Downregulation of Klotho expression by dehydration. *Am J Physiol Renal Physiol.* 2011 Oct;301(4):F745-50.
44. Jurado-Fasoli L, et al. Alcohol consumption and S-Klotho plasma levels in sedentary healthy middle-aged adults: A cross sectional study. *Drug Alcohol Depend.* 2019 Jan 1;194:107-111.
45. Jurado-Fasoli L, et al. Relationship between dietary factors and S-Klotho plasma levels in young sedentary healthy adults. *Mech Ageing Dev.* 2021 Mar;194:111435.
46. Jurado-Fasoli L, Castillo M, Amaro-Gahete F. Dietary Inflammatory Index and S-Klotho Plasma Levels in Middle-Aged Adults. *Nutrients.* 2020 Jan 21;12(2):281.
47. Agudelo J, et al. Fish Oil Supplementation Reduces Inflammation but Does Not Restore Renal Function and Klotho Expression in an Adenine-Induced CKD Model. *Nutrients.* 2018 Sep 11;10(9):1283.
48. Nakamura K, et al. Eicosapentaenoic acid prevents arterial calcification in klotho mutant mice. *PloS One.* 2017 Aug 3;12(8):e0181009.
49. Kaushal D, Kansal V. Probiotic Dahi containing Lactobacillus acidophilus and Bifidobacterium bifidum alleviates age-inflicted oxidative stress and improves expression of biomarkers of ageing in mice. *Mol Biol Rep.* 2012 Feb;39(2):1791-9.
50. Tang R, et al. [Effect of cordyceps sinensis extract on Klotho expression and apoptosis in renal tubular epithelial cells induced by angiotensin II]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban.* 2009 Apr;34(4):300-7.
51. Hu Y, et al. Curcumin attenuates cyclosporine A-induced renal fibrosis by inhibiting hypermethylation of the klotho promoter. *Mol Med Rep.* 2016 Oct;14(4):3229-36.
52. Prud'homme G, et al. The anti-aging protein Klotho is induced by GABA therapy and exerts protective and stimulatory effects on pancreatic beta cells. *Biochem Biophys Res Commun.* 2017 Dec 2;493(4):1542-1547.
53. Karsono A, et al. Potential Antiaging Effects of DLBS1649, a Centella asiatica Bioactive Extract. *J Exp Pharmacol.* 2021 Aug 11;13:781-795.
54. Kim H, et al. Epigallocatechin-3-O-(3-O-methyl)-gallate-induced differentiation of human keratinocytes involves klotho-mediated regulation of protein kinase-cAMP responsive element-binding protein signaling. *Int J Mol Sci.* 2014 Apr 4;15(4):5749-61.
55. Dokumacioglu E, Iskender H, Musmul A. Effect of hesperidin treatment on α-Klotho/FGF-23 pathway in rats with experimentally-induced diabetes. *Biomed Pharmacother.* 2019 Jan;109:1206-1210.
56. Kartinah N, et al. Potential of Hibiscus sabdariffa Linn. in managing FGF21 resistance in diet-induced-obesity rats via miR-34a regulation. *Vet Med Sci.* 2022 Jan;8(1):309-317.
57. Lim S, et al. Ginseng increases Klotho expression by FoxO3-mediated manganese superoxide dismutase in a mouse model of tacrolimus-induced renal injury. *Aging.* 2019 Aug 10;11(15):5548-5569.

References

58. Nguyen B, et al. Theanine attenuates memory impairments induced by klotho gene depletion in mice. *Food Funct.* 2019 Jan 22;10(1):325-332.
59. Ter Braake A, et al. Magnesium prevents vascular calcification in Klotho deficiency. *Kidney Int.* 2020 Mar;97(3):487-501.
60. Matsuzaki H, Kajita Y, Miwa M. Magnesium deficiency increases serum fibroblast growth factor-23 levels in rats. *Magnes Res.* Jan-Feb 2013;26(1):18-23.
61. Ko J, et al. Melatonin attenuates cisplatin-induced acute kidney injury in rats via induction of anti-aging protein, Klotho. *Food Chem Toxicol.* 2019 Jul;129:201-210.
62. Piao S, et al. Influence of N-acetylcysteine on Klotho expression and its signaling pathway in experimental model of chronic cyclosporine nephropathy in mice. *Transplantation.* 2013 Jul 27;96(2):146-53.
63. Chu S, et al. Effect of resveratrol on the repair of kidney and brain injuries and its regulation on klotho gene in d-galactose-induced aging mice. *Bioorg Med Chem Lett.* 2021 May 15;40:127913.
64. Xu Q, et al. Tanshinone IIA elevates serum soluble klotho levels and decreases cardiovascular events in patients on maintenance hemodialysis: a prospective before-after study. *Ann Palliat Med.* 2020 Jul;9(4):2131-2140.
65. Voelkl J, et al. Zinc Inhibits Phosphate-Induced Vascular Calcification through TNFAIP3-Mediated Suppression of NF- κ B. *J Am Soc Nephrol.* 2018 Jun;29(6):1636-1648.