American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Klotho a Key Player in the Diseasome of Aging

Mike KS Chan[1,2], Michelle BF Wong[1,2], Yuriy Nalapko[3] Krista Casazza[4], Dmytro Klokol[1,2], Olha Nishkuma[1,2], Jonathan RT Lakey[4,5]*

[1]*European Wellness Biomedical Group, Klosterstrasse 205ID, 67480, Edenkoben, Germany*

[2]*European Wellness Academy, EU, Malaysia*

[3]*Bogomolets National Medical University, Department of Internal Medicine #2, Kyiv, Ukraine.*

[4]*University of California, Irvine- Department of Surgery, Irvine CA, USA.*

[5]*University of California, Irvine- Department of Biomedical Engineering, Irvine, CA, USA.*

***Corresponding author:** Jonathan RT Lakey, Departments of Surgery and Biomedical Engineering, University of California Irvine, USA.

To Cite This Article: *Mike KS Chan, Michelle BF Wong, Krista Casazza, Dmytro Klokol, Olha Nishkumai, Yuriy Nalapko, Jonathan RT Lakey*. Klotho a Key Player in the Diseasome of Aging. Am J Biomed Sci & Res. 2025 25(2) AJBSR.MS.ID.003313,* DOI: 10.34297/AJBSR.2025.25.003313

Received: December 29, 2024; **Published:** January 02, 2025

Keywords: Klotho, Age-related Disease, Neurodegenerative Disease, Inflammation, Chronic Kidney Disease, Cardiovascular Disease, Aging

Introduction

The 1997 report by *Kuro-o et al* [1] of a mutant mouse displaying a age-related degenerative phenotype across multiple organs and tissues, spurned significant interest and investigations. The use of animal models enabled the identification of the "Klotho" gene, with subsequent characterization of Klotho as one of a family of single-pass transmembrane proteins including α-, β-, and Υ- Klotho isoforms [2]. Contemporaneously, Klotho is described as a multifunctional protein with roles as both a membrane-bound co-receptor and a soluble circulating factor with functional involvement spanning endocrine regulation, cellular signaling, and modulation of oxidative stress. Soluble Klotho is generated by cleavage of the membrane-bound form, acting as a circulating hormone with systemic effects. The membrane-bound Klotho serves as a co-receptor for fibroblast growth factor 23 (FGF23), regulating phosphate and vitamin D metabolism. Klotho is required for high affinity binding of FGF23 to its receptor FGFR1 it is the resultant binary complex that constitutes the physiological receptor for FGF23. Specifically, the isoform Klotho identified as the FGF23 co-receptor was α-Klotho, which hereafter is termed Klotho.

Klotho is expressed mainly on the cell surface membrane of proximal and distal renal tubules. The relationship between Klotho and FGF23 is central to maintaining phosphate and mineral homeostasis. FGF23, a hormone secreted primarily by osteocytes, regulates phosphate and vitamin D metabolism by acting on the kidneys to reduce phosphate reabsorption and suppress the production of active vitamin D. For FGF23 to function effectively, it requires the presence of Klotho. This FGF23–Klotho axis ensures that serum phosphate levels remain within a narrow physiological range, protecting against hyperphosphatemia and its associated risks, such as vascular calcification. Klotho also has independent roles as an anti-aging protein, influencing oxidative stress, inflammation, and cellular senescence, further contributing to systemic homeostasis and longevity.

In pathological conditions such as Chronic Kidney Disease

(CKD), the FGF23–Klotho relationship becomes dysregulated. As kidney function declines, Klotho expression decreases, impairing the kidneys' ability to respond to FGF23. To compensate, FGF23 levels rise dramatically, leading to a state of secondary hyperparathyroidism, phosphate retention, and reduced active vitamin D synthesis. Elevated FGF23 is also directly linked to cardiovascular complications, including left ventricular hypertrophy. The decline in Klotho exacerbates these problems, as its protective effects against oxidative stress and vascular calcification are lost. This vicious cycle contributes to CKD progression and its systemic complications. Targeting the FGF23–Klotho axis through therapeutic interventions, such as αKlotho supplementation or modulation of FGF23 activity, holds promise for mitigating these effects and improving outcomes in CKD and other diseases characterized by FGF23–Klotho dysregulation. The objective of this review is to describe the role of Klotho as a regulator of health, an integral component in mitigating disease pathology, and potential role as therapeutic agent across various age-related conditions.

Established Functional Roles of Klotho in Maintenance of Health

- Regulates mineral metabolism (calcium, phosphate).
- Enhances antioxidant defenses by up-regulating FOXO transcription factors and reducing oxidative stress.
- Modulates insulin signaling and suppresses the insulin/IGF-1 pathway, linking it to longevity.
- Influences kidney function and prevents renal fibrosis.

Emerging Roles of Klotho in Maintenance of Health

- Protects against vascular calcification and promotes cardiovascular health.
- Plays a neuroprotective role by enhancing synaptic plasticity and cognition.
- Decreased Klotho expression contributes to CKD progression, vascular calcification, and cardiovascular disease.

Klotho Function is Tightly Correlated with the Pathogenic Mechanisms Underpinning Chronic Kidney Disease

Chronic kidney disease (CKD) is a progressive, systemic condition. CKD affects approximately 10–12% of the global population. CKD prevalence continues to increase due to an aging demographic and the increasing incidence of obesity and type 2 diabetes (T2D). The progressive loss of kidney function leads to a range of systemic complications, including persistent low-grade inflammation, hyperphosphatemia, cardiovascular disease (CVD), anemia, hypertension, mineral and bone disorders, muscle wasting, osteoporosis, and frailty [3]. In early CKD stages, reduced renal phosphate reabsorption increases FGF-23 secretion to enhance phosphate excretion. However, by stage 3 CKD, hyperphosphatemia becomes systemic, exacerbating inflammation and vascular calcification (VC), contributing to early vascular aging (EVA) [4]. Hyperphosphatemia further induces endothelial dysfunction and activates the pro-inflammatory NF-κB pathway [5]. Additionally, declining renal function leads to nitrogenous waste accumulation, fueling persistent inflammation and a dysregulated immune system characterized by simultaneous immune activation and suppression [6].

A decade after the initial discovery of the Klotho gene (1997) in a mouse strain exhibiting vascular calcification, cardiac hypertrophy, osteopenia, and a shortened lifespan Klotho was found to function as a co-receptor for FGF23, an essential regulator of phosphate homeostasis [7]. Concurrently, hyperphosphatemia was recognized as a significant risk factor for cardiovascular morbidity and mortality. These insights, along with the subsequent identification of the FGF21–β Klotho axis, have established the FGF–Klotho system as a central regulator in CKD pathophysiology. Emerging research also highlights the roles of the gut microbiome and Calciprotein particles (CPPs) as influential factors in CKD [8].

As a critical regulator in kidney function, Klotho regulates phosphate and calcium homeostasis via FGF23, while its soluble form exerts systemic effects, including antioxidative, anti-inflammatory, and anti-fibrotic actions. Emerging evidence suggests that Klotho deficiency not only reflects CKD severity but may also drive its pathogenesis, making it a potential biomarker and therapeutic target. Recombinant Klotho protein, gene therapy, and small molecules aiming to restore Klotho levels have shown promise in preclinical models of CKD [9], demonstrating improvements in renal function, reduction in fibrosis, and alleviation of systemic complications. However, challenges remain in translating these findings into clinical settings, including efficient delivery methods and long-term safety evaluations. Understanding Klotho's precise mechanisms in renal pathophysiology is essential to harness its therapeutic potential fully.

CKD also displays a uremic phenotype marked by complications like vascular stiffness, osteoporosis, muscle wasting, cognitive decline, depression, and frailty, which mirror age-related disorders [10]. The pathogenesis of premature aging in CKD is explained through four mechanisms: (i) chronic oxidative stress, inflammation (inflammaging), and imbalances in autonomic and circadian regulation; (ii) stress response activation that inhibits anabolic processes and increases tissue degradation; (iii) disease-related factors that accelerate aging; and (iv) impaired anti-aging mechanisms [11,12]. Persistent activation of these mechanisms exacerbates systemic complications, reinforcing the cycle of damage and dysfunction. Thus, Klotho has been implicated in the causal pathway linking CKD and premature aging.

The premature aging phenotype [13,14] driven by persistent low-grade inflammation, oxidative stress, and mitochondrial dysfunction, which are common features in other chronic diseases, particularly cardiovascular diseases. The "inflammaging" phenotype coupled with immune dysfunction activates the inflammasome signaling cytokines, Reactive Oxygen Species (ROS) and Damage Associated Molecular Patterns (DAMPs), which collectively sup-

press Klotho expression and loss of protective factors like Klotho. Oxidative stress further activates pathways like p38 and JNK, contributing to inflammation and cellular senescence. Uremic toxins, such as indoxyl sulfate, p-cresyl sulfate, and Advanced Glycation End Products (AGEs), exacerbate oxidative stress, mitochondrial damage, and endothelial injury, accelerating CKD progression and related complications.

Uremic inflammation in CKD is marked by aberrant innate immune system activation, particularly monocyte-driven cytokine synthesis, with elevated levels of IL-6, TNF, and IL-1β contributing to systemic inflammation [15,16]. Dysregulated inflammasome signaling and epigenetic, further exacerbate inflammation and renal fibrosis. Senescent cells in CKD adopt a Senescence-Associated Secretory Phenotype (SASP), amplifying the production of inflammatory cytokines and chemokines, thereby perpetuating the inflammatory state and premature aging processes [17-19]. This complex interplay of systemic inflammation, oxidative stress, and epigenetic dysregulation underscores the multifactorial pathophysiology of CKD and its association with accelerated aging and systemic complications.

Patients affected by CKD and Mineral Bone Disorder (CKD-MBD) have a High Risk of Cardiovascular Mortality that is Poorly Explained by Traditional Risk Factors

While the kidneys are the main source of soluble Klotho and as such the target organ of the various mineral metabolism-related effects of Klotho, the Klotho deficiencies observed in CKD induce vascular systemic manifestations including cardiovascular lesions. Cardiovascular diseases (CDV) characterized by vascular calcification [20], inflammation, endothelial dysfunction and oxidative stress are the leading cause of mortality in CKD patients. Klotho deficiency features medial calcification, intima hyperplasia, endothelial dysfunction [21,22], arterial stiffening, hypertension, impaired angiogenesis, and reduced vasculogenesis aging) [23]. Low Klotho has been associated with arterial stiffness [24] and coronary artery disease [25]. Given the speculation that Klotho is critical for vascular health and therapeutic administration exerts vasculo-protective effects in animal models, it is conceivable that Klotho may play a causal role in the pathogenesis of cardiovascular complications in CKD [26]. Klotho has been shown *in vitro* to decrease oxidative stress and apoptosis in both smooth muscle and endothelial cells, to reduce smooth muscle cells calcification, and maintain the contractile smooth muscle phenotype. Klotho has also been shown to activate the Renin Angiotensin System (RAS) and diminish expression of antioxidant defenses mediated by the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), thereby attenuating oxidative stress. However, the mechanisms by which Klotho may elicit a protective effect on vascular smooth muscle cell mitigating dysfunction elicited by Angiotensin II (AngII) is not known. Nonclinical models demonstrate that Klotho protein reduces the rate of apoptosis and improves the function of vascular endothelial cells [27]. However, no compelling evidence exists that delineates the effects of Klotho on the cardiovascular system.

Klotho expression levels and its circulating level decline during aging. Aging is characterized by the gradual accumulation of physiological and molecular deficits [28]. These deficits occur at varying rates across tissues, organs, and individuals, resulting in a dynamic state of progressive functional decline, increased frailty, and reduced metabolic flexibility. Aging is governed by distinct biochemical pathways and marked by significant changes in cell signaling, genomic instability, epigenetic dysregulation, loss of proteostasis, mitochondrial dysfunction, dysregulated nutrient sensing, and cellular senescence. In the context of Klotho, aging also involves phosphate toxicity, reduced nuclear factor erythroid 2-related factor 2 (Nrf2) expression [29], and microbial dysbiosis, collectively contributing to the "diseasome of aging," reflecting the molecular allostatic load, with particular emphasis on phosphate metabolism.

Klotho is expressed in the choroid plexus of the brain and controls the brain-immune system interface in the choroid plexus. Klotho expression levels and its circulating level decline during aging. Klotho is a pivotal regulator of aging, functioning as both a longevity gene and a modulator of age-related physiological decline. Its membrane-bound form acts as a co-receptor for fibroblast growth factor 23 (FGF23)14, regulating phosphate, calcium, and vitamin D homeostasis, while its soluble form exerts systemic effects by influencing oxidative stress, inflammation, and cellular signaling pathways. Klotho expression declines with age, and reduced levels are associated with various aging phenotypes, including cognitive decline, sarcopenia, osteoporosis, vascular calcification, and metabolic dysregulation. Mechanistically, Klotho enhances antioxidant defenses by activating FOXO transcription factors, suppressing insulin/IGF-1 signaling, and reducing cellular senescence. It also modulates inflammatory responses and maintains tissue integrity, particularly in the brain, kidneys, and cardiovascular system. Experimental models demonstrate that restoring Klotho levels extends lifespan and mitigates age-related diseases, underscoring its potential as a therapeutic target. Strategies such as recombinant Klotho protein, gene therapy, and small molecules mimicking its actions are being explored to counteract aging processes. However, challenges remain in fully elucidating a role for Klotho in complex aging networks, understanding its tissue-specific effects, and developing safe and effective interventions for clinical use. Klotho represents a promising avenue in the pursuit of healthy aging and longevity.

Klotho, the Gut-Brain Axis, Aging and Metabolic Disorders

The anti-aging protective effects of Klotho extend beyond its known role in phosphate homeostasis and aging. The evidence of modulation of inflammation and oxidative stress are critical to the health of the gut-brain axis [30,31]. Reduced Klotho levels can impair gut barrier function, promoting systemic inflammation, which is implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's [32]. Moreover, Klotho influences microbiome composition by mitigating dysbiosis, an imbalance in gut microbial communities that contributes to increased permeability and chronic low-grade inflammation [33]. These effects can cascade into the brain, exacerbating neuroinflammation and neuronal dysfunction.

The gut microbiota itself may regulate Klotho expression through microbial metabolites, further highlighting the interplay between these systems [34].

In the brain, Klotho enhances synaptic plasticity and supports cognitive function. It counteracts neuroinflammatory pathways mediated by reactive oxygen species and pro-inflammatory cytokines. The protein's interaction with FGF23, known for its endocrine effects, also connects metabolic regulation to the gut-brain axis. Understanding Klotho's role within this axis opens avenues for therapeutic strategies targeting age-related diseases, chronic kidney disease, and neurodegeneration through gut microbiota modulation, anti-inflammatory therapies, and Klotho-enhancing interventions.

Emerging evidence suggests that Klotho interacts with gut microbiota and influences metabolic outcomes via the gut-liver axis. This interaction impacts bile acid metabolism and lipid absorption, both critical in maintaining energy balance.

Specific to metabolic disorders, Klotho via mitigation of chronic inflammation and oxidative stress, the two key components of insulin resistance and cardiovascular complications are indirectly attenuated. Reduced Klotho levels are linked to the activation of pro-inflammatory pathways, including NF-κB signaling, exacerbating systemic inflammation observed in metabolic syndrome [35]. Furthermore, Klotho has protective effects on adipose tissue by promoting healthy adipogenesis and reducing ectopic fat deposition, which is often implicated in metabolic dysfunction. Therapeutic strategies aimed at enhancing Klotho expression or mimicking its activity are being explored as potential interventions for metabolic disorders. These therapies hold promise for addressing the underlying mechanisms of insulin resistance, dyslipidemia, and cardiovascular risk, offering a novel approach to managing metabolic diseases.

Neurodegenerative Diseases: Protective in Alzheimer's and Parkinson's disease Models by Reducing Inflammation and Improving Neural Resilience

Klotho plays a critical neuroprotective role in the context of neurodegenerative diseases, linking its functions in aging and systemic health to brain resilience. Expressed in the brain and peripheral tissues, both the membrane-bound and soluble forms of Klotho contribute to neuronal health by reducing oxidative stress, modulating inflammation, and maintaining calcium homeostasis. In neurodegenerative disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD) [36], and Amyotrophic Lateral Sclerosis (ALS), Klotho deficiency is associated with exacerbated neuronal damage, impaired synaptic plasticity, and cognitive decline. Mechanistically, Klotho enhances antioxidative defenses through FOXO transcription factors, reduces neuroinflammation by suppressing NF-κB signaling, and modulates pathways such as Wnt and IGF-1, which are dysregulated in these conditions. Preclinical studies show that Klotho supplementation or overexpression improves memory, reduces amyloid-beta and tau pathology in AD models, and enhances dopaminergic neuron survival in PD models. Its role in promoting neural stem cell function and myelin repair further underscores its therapeutic potential. Despite promising results, challenges remain in translating these findings to clinical applications, including the need for targeted delivery systems, understanding tissue-specific effects, and ensuring long-term safety. Klotho-based therapies represent a compelling avenue for combating neurodegenerative diseases, though further research is needed to address gaps in knowledge and optimize interventions.

Cancer: Klotho May act as a Tumor Suppressor in Cancers such as Breast and Colorectal Cancer by Inhibiting IGF-1 and Wnt Signaling Pathways

Klotho functions as a tumor suppressor in various cancers, exerting its effects through diverse molecular pathways that regulate cell proliferation, apoptosis, and inflammation. Initially identified for its role in aging, Klotho has been found to inhibit the progression of cancers such as breast, colorectal, lung, pancreatic, and renal cancers. Mechanistically, it suppresses oncogenic signaling pathways, including the insulin-like growth factor 1 (IGF-1), Wnt/β-catenin, and PI3K/Akt/mTOR pathways, which are commonly activated in cancer cells. Klotho also modulates the tumor microenvironment by reducing oxidative stress, mitigating chronic inflammation via NF-κB suppression, and enhancing cellular sensitivity to chemotherapeutic agents. Low Klotho expression is associated with tumor aggressiveness, metastasis, and poor prognosis in several cancer types.

Conversely, restoring Klotho expression through gene therapy or recombinant protein administration has demonstrated anti-cancer effects in preclinical models, including reduced tumor growth, enhanced apoptosis, and inhibition of epithelial-mesenchymal transition EMT. However, the dual role of Klotho as both a tumor suppressor and, in certain contexts, a potential promoter of cell survival raises challenges in its therapeutic application. Further research is needed to elucidate tissue-specific roles, optimize delivery methods, and understand its interaction with standard cancer therapies. Klotho represents a promising but complex target for cancer treatment, with the potential to complement existing therapeutic strategies.

Bridging the Gap Between Promising Preclinical Findings and Successful Human Trials

There is evidence, albeit largely preclinical, that represents both a geroprotective and senomorphic therapy serving to mitigate or inhibit the effects of macromolecular damage leading to loss of cellular function and suppress senescence effects without cytotoxicity. There is growing support for preclinical efforts to enhance Klotho expression using viral vectors or CRISPR-based strategies as well as drug discovery efforts for small molecules and peptides mimicking Klotho's actions. To date, studies have focused on mid- to late in the life course, with few (if any) robust evaluation in early

adulthood. Klotho remains a promising target for intervention in aging and age-related diseases. However, producing and utilizing Klotho as a therapeutic agent is both technically demanding and costly due to its nature as a membrane-bound protein. Moreover, elevated serum levels of Klotho can disrupt calcium and phosphorus balance, leading to conditions such as hypocalcemia and hypophosphatemia. However, studies have shown that targeting the KL1 domain alone is effective in inducing protective effects without affecting phosphate levels. This observation led European Wellness (EW) to hypothesize that small peptides derived from Klotho could be leveraged replicating the anti-diseasome effects while avoiding unwanted side effects.

Peptides function as signaling molecules, binding to receptors on cells to initiate processes such as migration, proliferation, and differentiation, with these effects varying based on the peptide sequence. When integrated into scaffolds, peptides enhance stem cell adhesion and support tissue regeneration in areas needing repair. Stem cell-derived peptides, short protein fragments derived or synthesized from stem cells, mimic the functions of native stem cell proteins and show potential in regenerative medicine by facilitating adhesion, proliferation, and differentiation, particularly for tissue repair. These peptides, sourced from various stem cells, including Mesenchymal Stem Cells (MSCs), accelerate wound healing by promoting cell migration and proliferation. Additionally, their anti-inflammatory properties may offer therapeutic value for inflammatory conditions. Peptides Emulating Extracellular Matrix (ECM) components further enhance cell adhesion and migration.

Cellular morphology and function influence the ultrastructure and tissue-specific production of biologically active substances, including peptides. Leveraging organ and tissue specificity, peptide therapies can reinvigorate cellular signaling, prompting either peptide synthesis or restoring normal signaling pathways, ultimately rejuvenating tissues and organisms. The short length and low molecular weight of peptides enable efficient large-scale synthesis, extraction, and distribution for therapeutic use.

Nano Organo Peptides (NOPs) and Mito Organelles (MO) peptides are extensively utilized in humans and animals. NOPs, approximately 3nm in size and weighing under 10kDa, are derived from mammalian stem cells using a proprietary multi-step ultrafiltration process. This ensures specificity by isolating substances under 10kDa. Their small size and high solubility allow administration via sublingual or injectable routes and have been explored for uses such as cosmetics and regenerative organ repair. In contrast, MO peptides, extracted from mitochondria-specific cellular components, focus on enhancing mitochondrial function. With aging, weakened mitochondrial signaling contributes to apoptosis and cellular decline. MO peptides aim to restore mitochondrial activity and promote cellular regeneration. Unlike NOPs, MO peptides are larger and tailored for mitochondrial revitalization.

Mitochondria are the core organelles producing the energy for any cell. In the kidney, heart, and brain mitochondrial dysfunction is detected at the pre-clinical stage of the disease. Thus, mitochondrial autophagy (mitophagy) is the high-sensitive test of the age-related dysfunction. Furthermore, mitochondrial dysfunction promotes ROS activation, peptide malfunction, cell damage and apoptosis. The number of peptides and polypeptides encoded by mtDNA is very small compared to that encoded by nuclear DNA. Therefore, mtDNA and mitochondria are vital for proper cellular function. Mitochondrial RNA contains information about the organ-specific peptides secreted by cardiomyocytes, fibroblasts, epicardium, endothelial cells, etc.

Peptides can also simulate growth factor activity to support cell proliferation and differentiation. EW has is currently investigating the potential therapeutic applications of stem cell-derived peptides in diabetes, especially type 1 diabetes (T1D), where they may replicate insulin-producing beta cells' functions, regulate blood sugar, and protect beta cells from immune damage. Given the integral link between T1D and CKD, Klotho peptides represent an auspicious area of investigation. The EW group evaluated peptide therapy products from EW and the BioPep Research Group, which developed NOP and MO peptides using a proprietary extraction process. In a study on NOD mice, intramuscular administration of MO peptides from thymus and pancreatic extracts twice weekly over 17 weeks aimed to delay or prevent beta-cell destruction in pancreatic islets. Furthermore, cytokine analysis revealed significant differences in erythropoietin (EPO) and chemokine ligand 5 (CCL5/RANTES) levels between MO-treated and control groups. MO peptide-treated mice showed higher average EPO (374.88 pg/mL vs. 203.68 pg/mL, $p = 0.0062$) and CCL5 (14.37 pg/mL vs. 8.08 pg/mL, $p = 0.031$) concentrations. These findings provide promising preliminary evidence that MO peptides may delay T1D onset and merit further investigation as a novel therapeutic approach. Importantly, these pathways overlap in the inflammatory cascade observed in uremic inflammation.

Thus, Klotho-derived peptides, hold significant promise in regenerative medicine due to their ability to mimic natural biological functions. NOPs and MO peptides further expand therapeutic possibilities by targeting tissue-specific or mitochondrial functions, promoting cellular rejuvenation, and restoring organ vitality. These peptides, including MO peptides' ability to delay beta-cell destruction in diabetes and Klotho peptides' anti-aging effects, represent a convergence of regenerative and protective strategies. By integrating these approaches, peptide therapies could transform treatments for aging, diabetes, and degenerative diseases through targeted repair and systemic revitalization.

Acknowledgement

None.

Conflict of Interest

None.

References

1. Kuro o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, et al (1997) Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature 390(6655): 45-51.

2. Kuro-O M (2019) The Klotho proteins in health and disease. Nat Rev Nephrol 15(1): 27-44.
3. Wei X, Huang X, Liu N, Qi B, Fang S, et al (2021) Understanding the Stony Bridge between Osteoporosis and Vascular Calcification: Impact of the FGF23/Klotho axis. Oxid Med Cell Longev 7536614.
4. Yu L and Li M (2020) Roles of klotho and stem cells in mediating vascular calcification (Review). Exp Ther Med 20(6): 124.
5. Jin M, Lv P, Chen G, Wang P, Zuo Z et al (2017) Klotho ameliorates cyclosporine A-induced nephropathy via PDLIM2/NF-kB p65 signaling pathway. Biochem Biophys Res Commun 486(2): 451-457.
6. Fitzpatrick EA, Han X, Xiao Z and Quarles LD (2018) Role of Fibroblast Growth Factor-23 in Innate Immune Responses Front Endocrinol 9: 320.
7. Kurosu H and Kuro O M (2009) The Klotho gene family as a regulator of endocrine fibroblast growth factors. Mol Cell Endocrinol 299(1): 72-78.
8. Kuro O M (2021) Klotho and calciprotein particles as therapeutic targets against accelerated ageing. Clin Sci Lond Engl 1979 135(15): 1915-1927.
9. Buchanan S, Combet E, Stenvinkel P and Shiels PG (2020) Klotho, Aging, and the Failing Kidney. Front Endocrinol 11: 560.
10. Edmonston D, Grabner A and Wolf M (2024) FGF23 and klotho at the intersection of kidney and cardiovascular disease. Nat Rev Cardiol 21(1): 11-24.
11. Abraham C and Li A (2022) Aging-suppressor Klotho: Prospects in diagnostics and therapeutics. Ageing Res Rev 82: 101766.
12. Castner SA, Gupta S, Wang D, Moreno AJ, Park C, et al (2023) Longevity factor klotho enhances cognition in aged nonhuman primates. Nat Aging 3(8): 931-937.
13. Kuro o M (2009) Klotho and aging. Biochim Biophys Acta 1790(10): 1049-1058.
14. Kuro O M (2021) Aging and FGF23-klotho system. Vitam Horm 115: 317-332.
15. Kooman JP, Dekker MJ, Usvyat LA, Kotanko P, Sande FMVD et al (2017) Inflammation and premature aging in advanced chronic kidney disease. Am J Physiol Renal Physiol 313(4): F938-F950.
16. Ebert T, Pawelzik SC, Witasp A, Arefin S, Hobson S, et al (2020) Inflammation and Premature Ageing in Chronic Kidney Disease. Toxins 12(4): 227.
17. Ebert T, Pawelzik SC, Witasp A, Arefin S, Hobson S, et al (2020) Inflammation and Premature Ageing in Chronic Kidney Disease. Toxins 12(4): 227.
18. Ebert T, Neytchev O, Witasp A, Kublickiene K, Stenvinkel P, et al (2021) Inflammation and Oxidative Stress in Chronic Kidney Disease and Dialysis Patients. Antioxid Redox Signal 35(17): 1426-1448.
19. He T, Xiong J, Huang Y, Zheng CH, Liu Y et al (2019) Klotho restrain RIG-1/NF-κB signaling activation and monocyte inflammatory factor release under uremic condition. Life Sci 231: 116570.
20. Lim K, Lu TS, Molostvov G, Lee CH, Lam FT, et al (2012) Vascular Klotho deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. Circulation 125(18): 2243-2255.
21. Donate Correa J, Martín Núñez E, Mora Fernández C, Muros de Fuentes M, Pérez Delgado N,et al (2015) Klotho in cardiovascular disease: Current and future perspectives. World J Biol Chem 6(4): 351-357.
22. Saito Y, Yamagishi T, Nakamura T, Ohyama Y, Aizawa H, et al (1998) Klotho protein protects against endothelial dysfunction. Biochem Biophys Res Commun 248(2): 324-329.
23. Iurciuc S, Cimpean AM, Mitu F, Heredea R and Iurciuc M (2017) Vascular aging and subclinical atherosclerosis: why such a "never ending" and challenging story in cardiology? Clin Interv Aging 12: 1339-1345.
24. Kitagawa M, Sugiyama H, Morinaga H, Inoue T, Takiue K, et al (2013) A decreased level of serum soluble Klotho is an independent biomarker associated with arterial stiffness in patients with chronic kidney disease. PloS One 8(2): e56695.
25. Jo SH, Kim SG, Choi YJ, Joo NR, Cho GY, et al (2009) KLOTHO gene polymorphism is associated with coronary artery stenosis but not with coronary calcification in a Korean population. Int Heart J 50(1): 23-32.
26. Mencke R, Hillebrands JL and NIGRAM consortium (2017) The role of the anti-ageing protein Klotho in vascular physiology and pathophysiology. Ageing Res Rev 35:124-146.
27. Cui W, Leng B and Wang G (2019) Klotho protein inhibits H2O2-induced oxidative injury in endothelial cells via regulation of PI3K/AKT/Nrf2/HO-1 pathways. Can J Physiol Pharmacol 97(5): 370-376.
28. Prud'homme GJ, Kurt M and Wang Q (2022) Pathobiology of the Klotho Antiaging Protein and Therapeutic Considerations. Front Aging 3: 931331.
29. Donato AJ, Machin DR and Lesniewski LA (2018) Mechanisms of Dysfunction in the Aging Vasculature and Role in Age-Related Disease. Circ Res 123(7): 825-848.
30. Pluznick JL (2020) The gut microbiota in kidney disease. Science 369(6510):1426-1427.
31. Onal EM, Afsar B, Covic A, Vaziri ND and Kanbay M (2019) Gut microbiota and inflammation in chronic kidney disease and their roles in the development of cardiovascular disease. Hypertens Res Off J Jpn Soc Hypertens 42(2): 123-140.
32. Chen P, Tang Y, Luo L, Chen H and He X (2023) Lower serum Klotho level and higher systemic immune-inflammation index: an inverse correlation. BMC Geriatr 23(1): 650.
33. Wu L, Yan Q, Chen F, Cao C and Wang S (2021) Bupleuri radix extract ameliorates impaired lipid metabolism in high-fat diet-induced obese mice via gut microbia-mediated regulation of FGF21 signaling pathway. Biomed Pharmacother Biomedecine Pharmacother 135: 111187.
34. Lai L, Li Y, Liu J, Luo L, Tang J, et al (2021) Bovine serum albumin aggravates macrophage M1 activation and kidney injury in heterozygous Klotho-deficient mice via the gut microbiota-immune axis. Int J Biol Sci 17(3): 742-755.
35. Cheng YW, Hung CC, Fang WH and Chen WL (2022) Association between Soluble α-Klotho Protein and Metabolic Syndrome in the Adult Population. Biomolecules 12(1): 70.
36. Gao X, Li Y, Sun Z, Xu H, Ma G, et al (2021) Could α-Klotho Unlock the Key Between Depression and Dementia in the Elderly: from Animal to Human Studies. Mol Neurobiol 58(6): 2874-2885.