



Klotho and disease-related with thyroid glands

Noor Abd Al-Hakeem Abdullah, Ekhlas Abdallah Hassan
Department of chemistry Science, College of science, Diyala University, Diyala, Iraq.

Article Info

Article history:

Received 12, 15, 2024
Revised 01, 18, 2025
Accepted 02, 19, 2025
Published 10, 30, 2026

Keywords:

α -Klotho
aging
thyroid gland
hyperphosphatemia
Vitamin D

ABSTRACT

Thyroid cancer and various endocrine disorders are associated with the multifunctional protein known as α -Klotho, also referred to as Klotho. However, nothing is known about the connection between blood Klotho levels and thyroid hormones. Additionally, mice homozygous for a hypomorphic Klotho gene (kl/kl) were the first to exhibit anti-aging capabilities. These mice exhibit vascular calcification, cardiac enlargement, hypertension, lung disease, kidney disease, multiorgan atrophy, fibrosis, hyperphosphatemia, hypercalcemia, stunted development, and a shorter lifetime. Klotho overexpression has the opposite effect and lengthens life.

Klotho levels in humans decrease with age, diabetes mellitus (DM), Alzheimer's (AD), and chronic kidney disease, with another diseases. The brain, pancreas, and other tissues also produce it., the kidneys are the primary source. Human kidney function frequently declines with age, lowering Klotho levels. This is associated with a higher death risk from all causes, and a shortage of Klotho causes hyperphosphatemia and hypervitaminosis D. Interestingly, Klotho inhibits four pathways: transforming growth factor β (TGF- β), insulin-like growth factor-1 (IGF1), Wnt and Nf-KB that link to aging in different methods.

These may induce cellular senescence, apoptosis, inflammation, immunological disorders, fibrosis and neoplasia. Accordingly, preclinical Klotho treatment improved cancer, diabetes, cardiovascular, renal, and neurological illnesses. In this article, we give a summary of recent advancements in the molecular mechanisms of α -Klotho protein, elucidating the part that α -Klotho protein plays in thyroid dysfunction and pointing out areas that need more research.

This is an open access article under the [CC BY](#) license.



Corresponding Author:

Ekhlas Abdallah Hassan

Department of chemistry Science, College of science ,University of Diyala,
Baqubah City, Diyala Governorate, Iraq.

Email: ekhlasbiochemistry@gmail.com



1. INTRODUCTION

Almost every tissue and organ in the body changes with age, leading to debilitating and/or deadly illnesses like cancer, chronic organ failure, cardiovascular disease, and neurodegeneration. Different species age at different rates, which may indicate a biological clock is poorly defined. Despite extensive research, molecular pathways driving aging remain poorly understood. However, age-related disorders most likely have a complex etiology. A tiny amount of genes in humans directly linked to either longevity [1] or accelerated aging, such as in progeria is an uncommon illness [2].

The antiaging gene Klotho (kl) and it's associated with Protein α -Klotho (also known as Klotho or KL) are focus of this review. In 1997, the gene was initially discovered in mice [3]. Mutated mice with a hypomorphic Klotho allele (Kl kl-kl) [3] or total deletion of the Klotho gene (Kl -/-) [4] demonstrate a condition with numerous aging hallmarks when the protein is lacking.

Mice with Klotho deficiencies show developmental delay, renal illnesses, hyperphosphatemia, hypercalcemia, vascular calcification, and cardiac enlargement, and hypertension, fibrosis of an organ, multiorgan atrophy, osteopenia, lung illnesses, cognitive dysfunction, and brief lifetime. [5, 6, 7]. Gene overexpression, on the other hand, extends the duration of survival [8].

Klotho can be the soluble endocrine mediator that has a range of functions [9, 10] (Figures 1, Figure 2, and Figure 3), or a membrane-bound FGF-23 coreceptor[11]. Klotho insufficiency and hyperphosphatemia, which are caused by age-related declines in renal function, are major contributors to the aging phenotype [12]. Klotho increases phosphate removal and safeguards the kidney (phosphaturic action). Klotho has a significant impact on a number of biology processes related to the aging and illness (Figure 4):

1. FGF-23 dependent control of calcium, vitamin-D and phosphate.
2. Anti-inflammatory and also antioxidant properties.
3. Preventing chronic fibrosis.
4. Preventive measures against heart illnesses.
5. Tumor suppressor (anti-cancer) actions.
6. Diabetes-related metabolic regulatory processes.
7. Anti-senescence and anti-apoptotic properties; maintenance of stem cells.
8. Protection from neurological diseases, such as Alzheimer's.

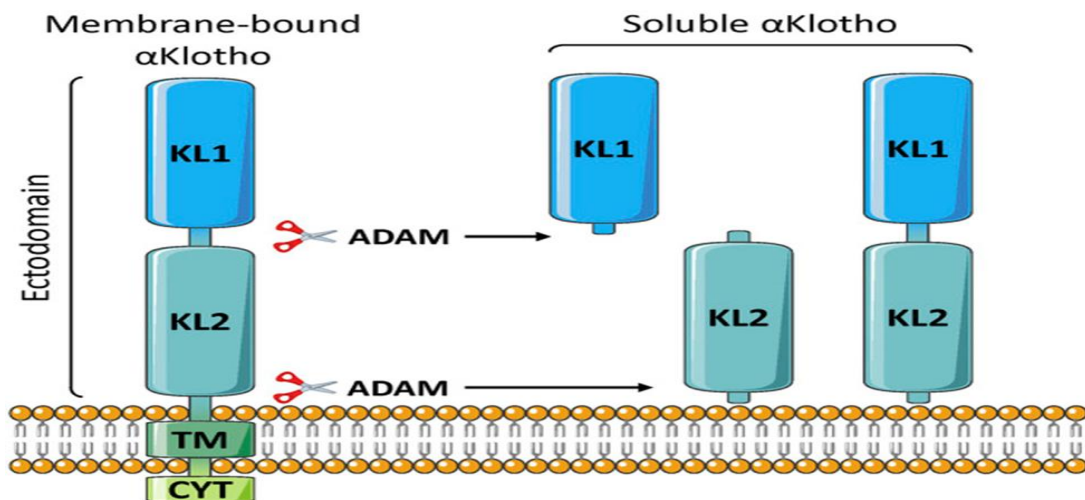


Figure 1.[13] klotho structure.

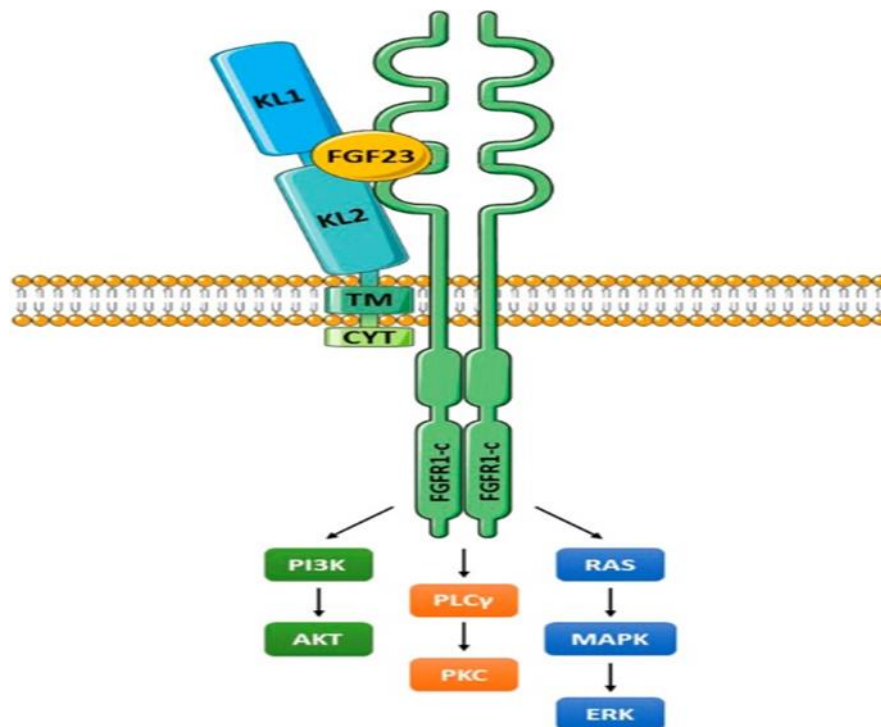


Figure 2. [14] Klotho, FGFR, and FGF-23 signaling complex

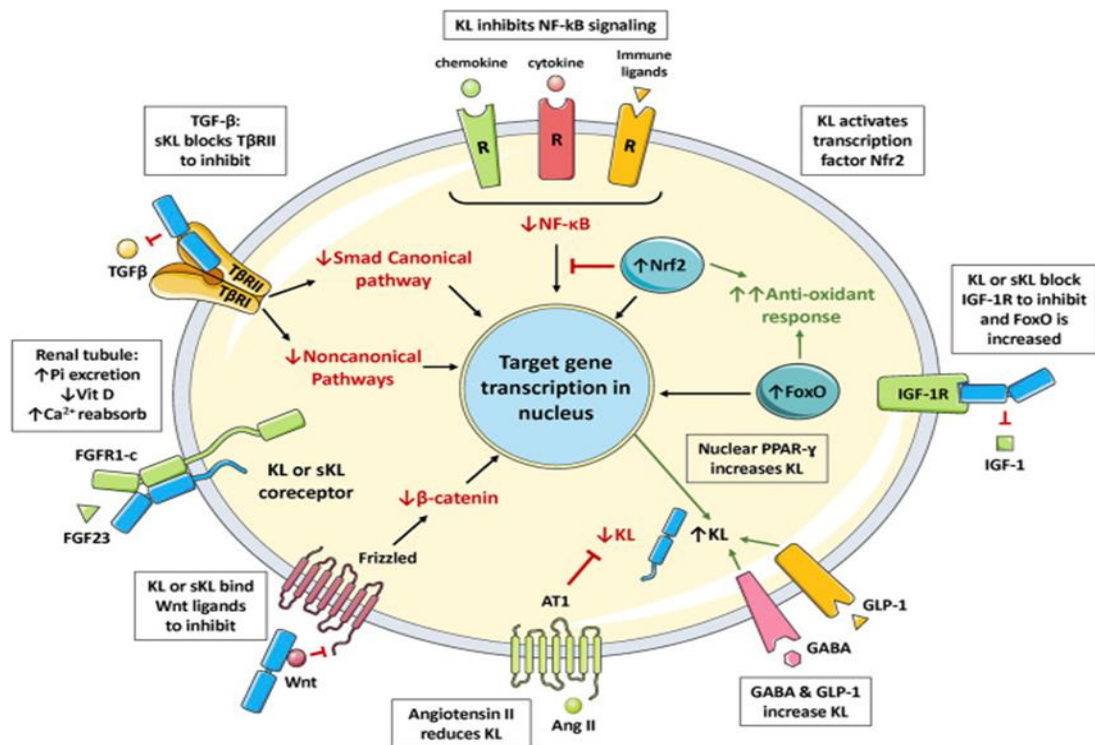


Figure 3. [15] The multiple functions of Klotho.

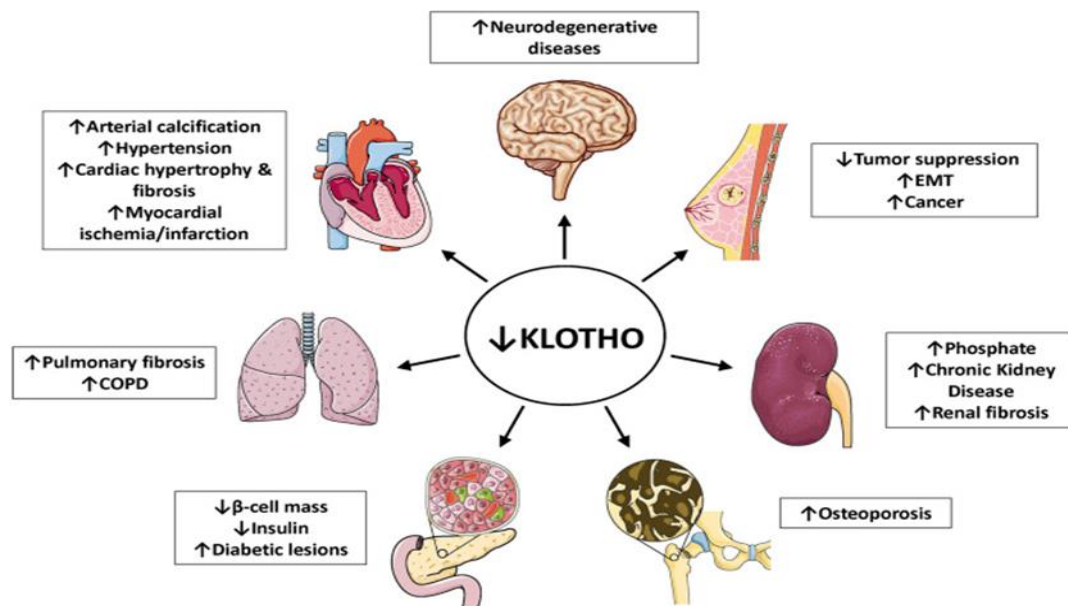


Figure 4. [16] Klotho deficiency is associated with a variety of age-related illnesses.

2. Klotho Production Sites:

Klotho is produced by several organs, including the kidney, brain, pancreatic β cells, blood arteries, and skin [17]. Additionally, expression has been reported in peripheral blood circulating cells in recent research [18]. Urine is another method of elimination. According to studies on mice with Klotho-specific genetic deletions [19] and nephrectomized rats [20], the kidney is the principal source of circulating Klotho. Both renal tubules (proximal and distal) generate it, with the distal tubule perhaps producing more of it [21]. Nevertheless, several [22][6] comparable levels of the membrane-bound form at both sites. Remarkably, Klotho has distinct purposes in the distal and proximal tubules [22].

Klotho increases Ca^{2+} reabsorption in the distal tubule while promoting a phosphatic effect and inhibiting vitamin-D synthesis in proximal tube. The significance of proximal tubular functions was confirmed by conditional inactivation of the Klotho gene in the proximal tubule, which reproduces many features of systemic gene inactivation [23].

3. Regulation and Molecular Features:

3.1 Soluble and Membrane-Bound Forms

Klotho is a 1,012 aa (130 kDa) single-pass membrane protein that has a very brief intracytoplasmic region (10 aa) in humans [24][25]. KL1 and KL2, the two domains that together make up the extracellular component, are shown in Figure 1. Membrane proteases, namely ADAM-10 and ADAM-17 (α secretases), can release soluble alpha-Klotho (soluble-Klotho) into bodily fluids to serve as an endocrine hormone [9].

Additional cleavage may result in the release of smaller KL1 or KL2 fragments, which never found in the blood circulation. It might be an additional soluble version of Klotho, believed to be produced by alternative splicing, that only contains KL-1 and is referred to as secreted Klotho. Nevertheless, there are early stop codons in the sequence, resulting in mRNA destruction [26].

The KL1/KL2 form of soluble Klotho, which is created by proteolytic cleavage of the membrane-bound protein (excretion), seems to contain the majority, if not all, of the protein. Indeed, secretase inhibitors that facilitate this proteolytic cleavage significantly reduce soluble -Klotho levels in circulatory system of mice [20].

Klotho shedding regulations are not fully established, although the role of alpha-secretase ADAM-10, ADAM-17 is well known, notably in renal tubular epithelial cells [27]. Insulin, growth hormones, and cytokines can all increase the expression levels of these enzymes. [28].

Tissue metalloproteinase inhibitors (TIMPs), on the other hand, prevent ADAM proteins from performing their functions. Certain medications may boost Klotho's proteolytic cleavage. Although there aren't many examples in research, ligustilide is an important example. In a mouse model of AD, this natural substance was protective and increase the expression of ADAM-10 and soluble-Klotho [29]. A wide range of biological processes may be impacted by the ADAM secretase proteins, which have a huge number of substrates. As a result, medications that target these enzymes are likely to be ineffective and harmful.

Klotho's crystal structure and bind site to the FGF receptor (particularly FGFR1c and FGF23) have been published [25]. No particular s-Klotho receptor has been found. However, it interacts to broadly distributed receptors on numerous cell kinds, including FGFR-s and the TGF- β receptor.

3.2 The Control of Klotho Expression:

The expression of Klotho is influenced by several variables [24]. This may vary greatly amongst tissues and is only poorly understood. Several variables, including circulatory stress, DM, hypertension, can modify Klotho expression in the primary source of synthesis. Klotho is frequently low in inflammatory illnesses and could be a valuable biomarker of inflammation [30].

Klotho gene expression is regulated by many transcription factors, including those that bind to promoter sites PAX4, Oct-1, Ap-2, E-box and Sp1 [24].

PAX4 serves as a positive regulator. The gene's 5' flanking region contains PPAR- γ response elements that enhance transcription. Diabetes is connected to the genes PAX4 and PPAR- γ . Vitamin-D binds to vitamin-D response sites in the promoter, resulting in Klotho transcription. In contrast, NF- κ B binds to the Klotho promoter but suppresses it [31] [32]. This might help to explain why inflammatory diseases have decreased amounts of Klotho. Notably, angiotensin-II inhibits Klotho transcription strongly (Figure-3), which has been connected to control of the positive regulator Sp-1 [33].

β -Hydroxy β -methylglutaryl-CoA (HMG- CoA) reductase is also inhibitory, statin medications are able to counteract that inhibit this enzyme [34][35] (Table 1). Statins increase Klotho m-RNA, potentially by deactivating Rho-A and/or decreasing the angiotensin-II response [36]. Interestingly, FGF-23 is the powerful negative regulator of Klotho transcription [37]. Thus, incidents that enhance FGF-23 production, such as chronic renal illness, will lower Klotho. Cancer cells frequently turn off the Klotho gene, which could be due to a variety of processes.

GC-rich and susceptible to DNA methylation, the Klotho promoter in particular can be rendered inactive in malignant tumors by DNA hypermethylation. miRNAs, which seem to play a significant role in cancer, also control Klotho [38].

Table 1. Example of current therapeutic medicines that increase Klotho levels.

Drugs	Clinical applications
RAAS inhibitors (Valsartan and losartan.)	-Chronic kidney disease(CKD)[39] -Diabetic[40] -nephropathy(DN)[41] -Hypertension[1]
PPAR-γ agonists (rosiglitazone, ciglitazone, pioglitazone)	-Diabetes Mellitus(DM)[42] - Hyperlipidemia[43]
Vitamin (D)	-Vitamin- D[44] -Hypocalcemia[45] -Rickets[46] -Osteoporosis[4]
Metformin	-Type2 diabetes[47]
Antiplasmodial (dihydroartemisinin)	-Malaria[48]
Endothelin-1 receptor antagonist (Atrasentan)	-Diabetic nephropathy(DN)[49]
Statins	-Ischemic[31] -cardiovascular and kidney disease[3]

4. The Klotho interactions between FGFRs and FGF23:

Klotho's extracellular domain creates a high-affinity receptor for FGF-23 by binding to FGFR-1c, -3c, or -4, all of which are tyrosine kinase receptors (Figure -2)[25][11].

FGF-19, FGF-21, and FGF-23 are commonly referred to as endocrine FGFs (e-FGFs) due to their solubility, ability to penetrate the circulation, and remote function. In contrast, tissue inhibitors of metalloproteinases (TIMP-s) prevent ADAM proteins from working [50].

Some medications can increase Klotho's proteolytic cleavage. There are few cases reported, but drug (ligustilide) is a remarkable exception. In a mouse model, this natural chemical boosted the expression of ADAM-10 and soluble-Klotho while also protecting against Alzheimer's disease [31]. Klotho's renal physiological activities have been well investigated [51].

In the kidney, FGFR-1c activation controls the exchange of calcium (Ca^{+2}) and phosphate. This is accomplished by blocking the proximal renal tubule's sodium phosphate transporters (NPT-2a and NPT-2c), which lowers the reabsorption of inorganic phosphate (Pi)(phosphatic effect)[52].

Ca^{+2} resorption via TRPV-5 channels is increased in the distal convoluted tubule. The distal tubule absorbs more Na^{+} due to increased $\text{Na}^{+}\text{Cl}^{-}$ cotransporter expression (NCC). FGF-23 /Klotho /FGFR1c decreases 1- α -hydroxylase expression in the proximal convoluted tubule (PCT), inhibiting the synthesis of active vitamin- D, also known as 1-25 (OH) 2D_3 . Among others advantages, vitamin- D stimulates calcium(Ca^{+2}) and phosphate absorption in the intestines, which will be decrease .Also,FGF-23 suppresses parathyroid hormone (PTH) production in a Klotho-independent way, influencing phosphate and calcium balance[53].

In mice, lacking Klotho or FGF-23 leads to increase the activity of 1- α -hydroxylase, overproduction of active vitamin-D and hypercalcemia / hyperphosphatemia.

In animals with Klotho deficiencies, hypervitaminosis-D and hyperphosphatemia seem to be linked to an accelerated aging phenotype [12][54]. A low-phosphate diet, however, improves illness even when vitamin D levels increase, indicating that hyperphosphatemia plays a larger role in the aging syndrome than vitamin D toxicity. Nonetheless, inhibiting vitamin-D responses reduced the lesions of Klotho deficient animals.

Calcium and phosphate ion hypersaturation in the blood leads to the formation of calciprotein particles (CPP-s). The CPP-s are thought to hasten the aging-related degenerative processes since they precipitate in tissues. Klotho shortage is commonly caused by renal failure, which can occur as a result of a variety of acute or chronic diseases. Rare human mutations that result in a significant deficit of either Klotho or FGF-23 are linked to hyperphosphatemia from an early age [55].

Calcification is widespread in the soft tissues, blood vessels, and numerous organs and anatomical locations throughout the body. Treatment options include a low-phosphate diet, phosphaturic medicines, medication for inflammation and phosphate binding agents.

This severe congenital deficit of either functional Klotho or FGF-23 is not similar to the substantially lower Klotho expression observed in the chronic disorders discussed in the study. Indeed, they are not linked to the extensive calcification seen in congenital hyperphosphatemia.

5. Klotho Functions independent of FGF23:

5.1 Inhibiting IGF1 Pathways:

Aging has long been linked to the insulin receptor/IGF1 signaling pathway, which is nutrient-sensitive [56][57]. Activation of the downstream mediator known as mechanistic target of rapamycin (mTOR) occurs when nutrients are plentiful, which has been associated to a number of age-related illnesses. Calorie restriction (CR) may lessen the damage and potentially lengthen life in some animals [58][59]. Therefore, Klotho's suppression of the IGF-1 /PI3K /Akt/ mTOR pathway is particularly important [60].

This is one possible mechanism via which Klotho produces anti-aging effects and protects against degenerative illnesses. In this situation, soluble-Klotho inhibits insulin/IGF1 receptor activation, which prevents downstream signaling processes such as IRS phosphorylation and PI3K / Akt / mTOR signaling. Rapamycin, a mTOR inhibitor, slows age-related illness in mice, including vascular calcification, while also increasing Klotho expression [61].

The insulin/IGF-1 pathway contributes to cancer development, while Klotho inhibits it. The insulin/IGF1 pathway is linked to anti-oxidant processes via the FoxO forkhead transcription factors (FOXOs). The Insulin/IGF1 pathway blockage causes FOXOs to migrate to the nucleus and production of numerous genes that produce enzymes that are antioxidants, including manganese superoxide dismutase [62]. As a result, mice that overexpress Klotho exhibit greater levels of FOXO activation than those that lack it.

6. Diabetes mellitus and obesity effects:

Remarkably, diabetics' islets have less Klotho [63]. Numerous researchers have documented decreased levels of Klotho in the bloodstream of individuals with type-1 diabetes (T1D) [64][65] and type-2 diabetes (T2D), especially when the condition is advanced [66]. Circulatory levels of soluble -Klotho are reduced in diabetic NOD mice (T1D) and db/db mice (T2D) [67].

Attenuation of FGFR1c, that expressed by β -cells, leads to diabetes with lower β cell numbers [68]. Islet cells express both Klotho and KLB, indicating that they can react to FGF-23 (Coreceptor Klotho) and FGF-21 (KLB coreceptor). FGFR1-c stimulates β cell signaling via many pathways (Figure 2), including P-13K/Akt for cell survival, RAS-MAPK for mitogenic response, and PLC-PPAR adiponectin for regulating glucose and lipid metabolism.

In mice, Klotho administered via gene transfer demonstrated notable protective effects on β cells in T-1D and T-2D models [69].

Klotho inhibited β -cell death and promoted their proliferation. The development of insulinitis in NOD mice is a significant pathological finding. The process starts with a peri- islet mononuclear cell infiltrate (including T- cells), then immune cell invasion, severe infiltration, and β cell death. The Klotho gene transfer inhibited insulinitis, implying an immunosuppressive and or anti- inflammatory impact. In db/db mice, recombinant Klotho also reduced hypertension and renal dysfunction [70].

7. Klotho as a Tumor Inhibitory:

Klotho has been shown to inhibit cancer-related pathways such as NF-KB, TGF- β , IGF1, and W-nt, supporting its role as a tumor suppressor [71] (Figure 3; Table 2). Klotho expression is reduced or suppressed in virtually all cancers studied [72].

Klotho-positive cancers often have a better prognosis. The Klotho appears to be suppressed using the same manner as other tumor suppressor genes. Examples of this include DNA hypermethylation at promoter sites, histone alterations, and mRNAs.

The Klotho has anti-tumor effects in experimental tumor models both in vitro and in vivo. Hepatocellular carcinoma (HCC), colon, stomach, and breast cancer have all been shown to exhibit this, as has pancreatic cancer [73] and breast cancer [74].

Klotho overexpression or s-Klotho treatment suppressed pancreatic cancer cell proliferation. Indeed, several searches have demonstrated that the Klotho suppresses cancerous cells reproduction, colony formation and invasion while promoting apoptosis and autophagy.

Similarly in vivo forced Klotho tumor overexpression or systemic s-Klotho treatment suppressed the development of various tumor types. This contains human cancers that have been xenografted onto mice. Klotho's membrane-bound and soluble versions both inhibit tumors.

[Table 2.](#) Klotho insufficiency and associated conditions.

Organ or system	Disease
Kidney.	-CKD[75] -Hyper-phosphatemia[76] -ischemic injury[20]
Brain.	-Alzheimer's disease[77]. -hippocampal -neuronal loss[78] -frailty[84]
Bone.	-Osteoporosis[10] -osteomalacia from CKD[79]
Cancer.	-Klotho protects against multiple cancer types[80]
Cardiovascular.	- Atherosclerosis[81] -- Cardiovascular hypertrophy [82] -Hypertension[83] - Myocardial ischemic infarct[84]
Lung.	- Respiratory fibrosis [85] - Chronic Obstructive Pulmonary Disorder[86]
Metabolism and diabetes.	- Type 1 and 2 diabetes include β -cell death[87] - glucose and lipid balance[88] - β cell regeneration[89] - autoimmune and inflammation (insulinitis)[90]

8. Neurodegenerative and Klotho Disorders:

Reduced amounts of Klotho are associated with neurological illnesses, cognitive infirmity [91], and frailty [92]. For example, among seniors home patients, low serum of Klotho was linked to cognitive infirmity, fragility, dependency and frequent falls[93]. Although Klotho's exact function in the brain is unknown, there is evidence that it has neuroprotective properties. The Klotho is generated by the choroid plexus and detected in cerebral spinal fluid. Additionally, the brain has high levels of its expression, especially in grey matter areas like the hippocampus. Age and the early stages of Alzheimer's disease cause a decrease in Klotho expression in the brain [94].

9. Alpha-Klotho with thyroid gland disorders:

The thyroid is one of the body's primary endocrine glands, producing thyroid hormones including thyroxine (T-4) and triiodothyronine (T-3)[95] almost all nucleated cells are impacted by thyroid hormones, which play crucial functions in the body [96][97]. Thyroid hormone control involves several molecules, including Na/I-ISO transporter protein(NIS), thyroglobulin(TG) , thyroid peroxidase (TPO), monoiodotyrosine (MIT), diiodotyrosine (DIT), and μ -Crystallin (CRYM)[98]. The development of thyroid cancers has been related to the klotho protein, according to recent studies[57] nevertheless, no research has been done on the connection between thyroid hormones and klotho protein. Klotho protein has multifunction that connected to a variety of endocrine illnesses including thyroid gland tumorigenesis and the klotho protein has been demonstrated to inhibit oxidative, infections and apoptotic processes, as well as control calcium and phosphorus metabolism.

Some studies found that poor expression of alpha-Klotho was implicated in thyroid tumor development and fT3 levels may be positively linked with soluble-Klotho concentrations [99]. T3 dramatically raised membrane form expression of the klotho gene [100]. Based on the research presented above, it has been suggested that klotho protein is connected with thyroid cancer and fT3, although the relationship between klotho protein and thyroid hormones and how it is associated has yet to be determined.

10. Strategies for Klotho-Based treatment:

10.1 Pharmacological treatments for a range of illnesses

Given the advantages Klotho's resistance to aging and illnesses, as demonstrated in preclinical models (Figure-4; Table-2), it is of great interest to develop uses in humans. Plasma Klotho levels in humans have been shown to decline with age and in prevalent illnesses such as CKD, DM and neurological disorders because of this the logical and safe objective would be to restore normal ranges ,so a few medications have already been recognized as having potential use in particular disorders.

In several of studies presented (Tables-1 and-3) the major impact was a rise in Klotho levels that approached or equaled normal, rather than exceeding normal. Based on mouse research, overexpression may lengthen longevity, but the safety is uncertain because other variables (such as insulin resistance) may emerge. It should be noted that almost all of the data on Klotho-based therapy has been gathered from rats.

Table 3. supplements, medications under preclinical research, or other treatments that raise Klotho.

Name	Diseases to be targeted
GABA receptor agonist	- Diabetic preclinical models [101] - Organ damage from streptozotocin [102]
Recombinant protein (s-Klotho, Klotho peptide, KL1)	-Preclinical diabetes[103] -metabolic[104] - renal[105] - vascular[105] -neurodegenerative[106]
Gene therapy and cell therapy (Klotho gene)	-Preclinical[107] - numerous illnesses (an alternative to recombinant protein therapy)[108]
Supplements, traditional medicines, and food (diet) components (tetrahydroxystilbene glucoside, ligustilide, resveratrol, cordycepin, curcumin, ginseng, astaxanthin, and baicalin)	Multiple indications and geroprotective[109]

A surprising variety of medicines raise Levels of Klotho in experimental animals (Tables-2 and 3), either in bloodstream or in particular organs. The literature has focused a lot of emphasis on a few of the compounds implicated as gero-protective substances [90],but their Klotho-inducing ability is seldom investigated. This contains multiple medications that are now in clinical trials for a variety of illnesses (Table 1).

10.1-1The vitamin D:

Supplementing with vitamin D increases Klotho levels, as observed in kids with CKD[97]. Children with mild to severe renal illness exhibited lower blood Klotho levels at the start of the research, which were corrected by the Vitamin-D medication. In contrast, patients with severe kidney illness showed unaltered the Klotho levels. This illustrates the little accessible data from clinical studies. However, there is strong evidence in rodents that vitamin-D enhances Klotho (Table 1). The complex relationships that control FGF-23/Klotho/vitamin-D homeostasis must be investigated in order to comprehend this therapeutic effect[58].

10.2 Physical activity and fitness:

Physical activity and sports are easy strategies for increasing circulating Klotho[110] found that one workout session temporarily increased amounts of circulating Klotho. The relationship between middle-aged sedentary persons' plasma levels of soluble-Klotho and physical activity and fitness was examined in the FIT-AGEING trial.

Higher exercise and fitness, according to the scientists, were related with greater s-Klotho levels. They evaluated the impact of several exercise programs during a 12-week span and found that all forms raised the Klotho when compared to no exercise. They found that more soluble-Klotho is associated with more lean mass and less fat[110].

11. Conclusions and Prospects for the Future:

The several aspects of Klotho biology were investigated in this review. Phosphate and Ca²⁺ balance are the most well-studied components of renal physiology. The significance of the interaction between FGF-23, Klotho, and FGFR was shown in mice lacking Klotho. The primary findings were hypervitaminosis-D and hyperphosphatemia. A low-phosphate diet significantly reduced these mice's accelerated aging syndrome. Humans with rare mutations of Klotho or FGF-23 have a hyperphosphatemic disease marked by significant tissue calcification and systemic inflammation. Klotho production is reduced in chronic renal illness of many etiologies, including diabetes. Deteriorating renal function and low Klotho have been linked to the acceleration or worsening of several age-related illnesses, including the Cp/CPP-s precipitation in tissue.

Klotho is characterized as an anti-aging substance, however there is no clear proof that it slows aging in people however, there are lots major ways for future development. This is one of the most crucial issues to answer, but it will take extensive research. Klotho can function as both a disease marker (the brain, kidney, or another) and a medicinal compound.

Klotho's functions in the brain, particular, remain unclear, however there are clear neuroprotective benefits and Klotho levels in the blood or brain fluid may indicate a person's susceptibility to sickness. Multiple medicines appear to enhance Klotho, although human research are limited. Does Klotho improve the effectiveness of some drugs used to treat diabetes mellitus, high blood pressure, high cholesterol, and transplant rejection? Are some of these drugs able to increase Klotho in order to cure neurodegenerative diseases? Nothing is known. There have been very few clinical trials on Klotho-related medicines outside of preclinical research. Another essential feature is Klotho's function as an inhibitor of tumor growth. Although this has been well-

documented in animals, a therapeutic atmosphere is required for its development. Klotho research's limited therapeutic uses may be due to a lack of understanding of its mechanisms of action, particularly outside the kidney. However, as shown in this review, our understanding of Klotho's molecular and physiological characteristics has advanced significantly in recent years.

Several therapeutic techniques are conceivable, as mentioned in this publication. Clinical study Given the relatively short half-life of these medications, it is necessary to develop long-acting structures or slow release formulations. The most straightforward method is to provide recombinant Klotho or peptides. Any of these approaches would be a significant addition to the field. Preclinical studies provide some indication that the Klotho injection is harmful, at least when normal range are restored. Though much more challenging, genetic treatment is potentially a possible option, and the long-term effects of supranormal levels are unclear.

Apart from some therapeutic prescription drugs, readily available over-the-counter medications, vitamins, and nutraceuticals can also increase Klotho. This is based on animal studies, and it would be quite interesting to investigate the possibilities of the Klotho augmentation in the people. In the case of neurodegenerative illnesses, it is important to note that several treatments, including some conventional therapies, might pass the blood-brain barrier and increase Klotho. Finally, exercising and maintaining fitness over time are simple ways to raise Klotho. To summarize, the majority of Klotho research has been conducted in the animal illness models, and before the Klotho therapy is applied to humans, a great deal of study needs to be done. This manuscript presents a set of hypotheses and information supporting clinical research on Klotho-based treatment.

ACKNOWLEDGEMENTS

My thanks and appreciation to the Head of the Department of Chemistry at the College of Science Asst.Prof. Dr. Wassan B.Ali and all the professors and staff of the Department of Chemistry.

REFERENCES

- [1] S. Javidnia, S. Cranwell, S. H. Mueller, C. Selman, J. M. Tullet, K. Kuchenbaecker, & N. Alic, "Mendelian randomization analyses implicate biogenesis of translation machinery in human aging", *Genome Research*, 32(2), 258-265(2022), DOI: [10.1101/gr.275636.121](https://doi.org/10.1101/gr.275636.121)
- [2] F. Coppède, "Mutations involved in premature-ageing syndromes", *The application of clinical genetics*, 279-295(2021), DOI: [10.2147/TACG.S273525](https://doi.org/10.2147/TACG.S273525)
- [3] M. Kuro-o, Y. Matsumura, H. Aizawa, H. Kawaguchi, T. Suga, T. Utsugi, Y. I. Nabeshima, "Mutation of the mouse klotho gene leads to a syndrome resembling ageing", *nature*, 390(6655), 45-51(1997), DOI: [10.1038/36285](https://doi.org/10.1038/36285)
- [4] H. Tsujikawa, Y. Kurotaki, T. Fujimori, K. Fukuda, & Y. I. Nabeshima, "Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system", *Molecular endocrinology*, 17(12), 2393-2403(2003), DOI: [10.1210/me.2003-0048](https://doi.org/10.1210/me.2003-0048)
- [5] P. Buendía, J. Carracedo, S. Soriano, J. A. Madueño, A. Ortiz, A. Martín-Malo, R. Ramírez, "Klotho prevents NFκB translocation and protects endothelial cell from senescence induced by uremia", *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, 70(10), 1198-1209(2015), DOI: [10.1093/gerona/glu170](https://doi.org/10.1093/gerona/glu170)
- [6] R. G. Erben, & O. Andrukhova, "FGF23-Klotho signaling axis in the kidney", *Bone*, 100, 62-68(2017), DOI: [10.1016/j.bone.2016.09.010](https://doi.org/10.1016/j.bone.2016.09.010)
- [7] S. Kinoshita, & M. Kawai, "The FGF23/KLOTHO regulatory network and its roles in human disorders", *Vitamins & Hormones*, 101, 151-174(2016), DOI: [10.1016/bs.vh.2016.02.001](https://doi.org/10.1016/bs.vh.2016.02.001)
- [8] H. Kurosu, M. Yamamoto, J. D. Clark, J. V. Pastor, A. Nandi, P. Gurnani, M. Kuro-o, "Suppression of aging in mice by the hormone Klotho", *Science*, 309(5742), 1829-1833(2005), DOI: [10.1126/science.1112766](https://doi.org/10.1126/science.1112766)
- [9] G. D. Dalton, J. Xie, S. W. An, & C. L. Huang, "New insights into the mechanism of action of soluble klotho", *Frontiers in endocrinology*, 8, 323(2017), DOI: [10.3389/fendo.2017.00323](https://doi.org/10.3389/fendo.2017.00323)
- [10] M. Kuro-o, "The FGF23 and Klotho system beyond mineral metabolism", *Clinical and experimental nephrology*, 21(Suppl 1), 64-69(2017), DOI: [10.1007/s10157-016-1357-6](https://doi.org/10.1007/s10157-016-1357-6)
- [11] I. Urakawa, Y. Yamazaki, T. Shimada, K. Iijima, H. Hasegawa, K. Okawa, T. Yamashita, "Klotho converts canonical FGF receptor into a specific receptor for FGF23", *Nature*, 444(7120), 770-774(2006), DOI: [10.1038/nature05315](https://doi.org/10.1038/nature05315)
- [12] M. Kuro-o, "A potential link between phosphate and aging—lessons from Klotho-deficient mice", *Mechanisms of ageing and development*, 131(4), 270-275(2010), DOI: [10.1016/j.mad.2010.02.008](https://doi.org/10.1016/j.mad.2010.02.008)
- [13] V. N. Vasilkova, I. Y. Pchelin, Y. A. Borovets, I. A. Vasukhina, & T. V. Mokhort, "Clinical significance of the T (-344) C polymorphism of the aldosterone synthase gene (CYP11B2) in the prognosis of cardiorenal syndrome in diabetes mellitus", *Health and Ecology Issues*, 19(4), 48-55.14(2023), DOI: <https://doi.org/10.51523/2708-6011.2022-19-4-07>
- [14] M. Akl, & A. Ahmed, "Unveiling the Interplay of Klotho Protein, Chemotherapy-Induced Klotho Protein Deficiency, and the Pivotal Role of GLP-1 Agonists like Ozempic in Cancer Survivorship Patient Survival Rate after Chemotherapy Treatment", 8 December (2023), DOI: [10.32388/EPHLKX](https://doi.org/10.32388/EPHLKX)
- [15] J. H. Park, E. S. Noh, & I. T. Hwang, "α-Klotho levels in girls with central precocious puberty: potential as a diagnostic and monitoring marker", *Frontiers in Endocrinology*, 15, 1383812(2024), DOI: [10.3389/fendo.2024.1383812](https://doi.org/10.3389/fendo.2024.1383812)
- [16] G. P. Dias, T. Murphy, D. Stangl, S. Ahmet, B. Morisse, A. Nix, S. Thuret, "Intermittent fasting enhances long-term memory consolidation, adult hippocampal neurogenesis, and expression of longevity gene Klotho", *Molecular psychiatry*, 26(11), 6365-6379(2021), DOI: [10.1038/s41380-021-01102-4](https://doi.org/10.1038/s41380-021-01102-4)

- [17] K. Lim, A. Groen, G. Molostvov, T. Lu, K. S. Lilley, D. Snead, D. Zehnder, "α-Klotho expression in human tissues", The Journal of Clinical Endocrinology & Metabolism, 100(10), E1308-E1318(2015), DOI: [10.1210/jc.2015-1800](https://doi.org/10.1210/jc.2015-1800)
- [18] E. Martín-Núñez, A. Pérez-Castro, V. G. Tagua, C. Hernández-Carballo, C. Ferri, N. Pérez-Delgado, J. F. Navarro-González, "Klotho expression in peripheral blood circulating cells is associated with vascular and systemic inflammation in atherosclerotic vascular disease", Scientific Reports, 12(1), 8422(2022), DOI: [10.1038/s41598-022-12548-z](https://doi.org/10.1038/s41598-022-12548-z)
- [19] K. Lindberg, R. Amin, O. W. Moe, M. C. Hu, R. G. Erben, A. Ö. Wernerson, T. E. Larsson, "The kidney is the principal organ mediating klotho effects", Journal of the American Society of Nephrology, 25(10), 2169-2175(2014) DOI: [10.1681/ASN.2013111209](https://doi.org/10.1681/ASN.2013111209)
- [20] M. C. Hu, M. Shi, J. Zhang, T. Addo, H. J. Cho, S. L. Barker, O. W. Moe, "Renal production, uptake, and handling of circulating αKlotho", Journal of the American Society of Nephrology, 27(1), 79-90(2016), DOI: [10.1681/ASN.2014101030](https://doi.org/10.1681/ASN.2014101030)
- [21] S. C. Lim, J. J. Liu, T. Subramaniam, C. F. Sum, "Elevated circulating alpha-klotho by angiotensin II receptor blocker losartan is associated with reduction of albuminuria in type 2 diabetic patients", Journal of the Renin-Angiotensin-Aldosterone System, 15(4), 487-490(2014), DOI: <https://doi.org/10.1177/1470320313475905>
- [22] O. Andrukhova, U. Zeitz, R. Goetz, M. Mohammadi, B. Lanske, & R. G. Erben, "FGF23 acts directly on renal proximal tubules to induce phosphaturia through activation of the ERK1/2-SGK1 signaling pathway", Bone, 51(3), 621-628(2012), DOI: [10.1016/j.bone.2012.05.015](https://doi.org/10.1016/j.bone.2012.05.015)
- [23] A. Takeshita, K. Kawakami, K. Furushima, M. Miyajima, & K. Sakaguchi, "Central role of the proximal tubular αKlotho/FGF receptor complex in FGF23-regulated phosphate and vitamin D metabolism", Scientific reports, 8(1), 6917(2018), DOI: [10.1038/s41598-018-25087-3](https://doi.org/10.1038/s41598-018-25087-3)
- [24] Y. Xu, Z. Sun, "Molecular basis of Klotho: from gene to function in aging", Endocrine reviews, 36(2), 174-193(2015), DOI: [10.1210/er.2013-1079](https://doi.org/10.1210/er.2013-1079)
- [25] G. Chen, Y. Liu, R. Goetz, L. Fu, S. Jayaraman, M. C. Hu, M. Mohammadi, "α-Klotho is a non-enzymatic molecular scaffold for FGF23 hormone signalling", Nature, 553(7689), 461-466(2018), DOI: <https://doi.org/10.1038/nature25451>
- [26] R. Mencke, G. Harms, J. Moser, M. van Meurs, A. Diepstra, H. G. Leuvenink, & J. L. Hillebrands, "Human alternative Klotho mRNA is a nonsense-mediated mRNA decay target inefficiently spliced in renal disease", JCI insight, 2(20), (2017), <https://doi.org/10.1172/jci.insight.94375>
- [27] E. P. van Loon, W. P. Pulskens, E. A. van der Hagen, M. Lavrijsen, M. G. Vervloet, H. van Goor, J. G. Hoenderop, "Shedding of klotho by ADAMs in the kidney", American Journal of Physiology-Renal Physiology, 309(4), F359-F368(2015), DOI: [10.1152/ajprenal.00240.2014](https://doi.org/10.1152/ajprenal.00240.2014)
- [28] M. Bzowska, N. Jura, A. Lassak, R. A. Black, & J. Bereta, "Tumour necrosis factor-α stimulates expression of TNF-α converting enzyme in endothelial cells", European Journal of Biochemistry, 271(13), 2808-2820(2004), DOI: <https://doi.org/10.1111/j.1432-1033.2004.04215.x>
- [29] X. Kuang, Y. S. Chen, L. F. Wang, Y. J. Li, K. Liu, M. X. Zhang, J. R. Du, "Klotho upregulation contributes to the neuroprotection of ligustilide in an Alzheimer's disease mouse model", Neurobiology of aging, 35(1), 169-178(2014), DOI: <https://doi.org/10.1016/j.neurobiolaging.2013.07.019>
- [30] S. E. Wu, & W. L. Chen, "Soluble klotho as an effective biomarker to characterize inflammatory states", Annals of medicine, 54(1), 1520-1529(2022), DOI: <https://doi.org/10.1080/07853890.2022.2077428>
- [31] J. A. Moreno, M. C. Izquierdo, M. D. Sanchez-Nino, B. Suarez-Alvarez, C. Lopez-Larrea, A. Jakubowski, A. B. Sanz, "The inflammatory cytokines TWEAK and TNFα reduce renal klotho expression through NFκB", Journal of the American Society of Nephrology, 22(7), 1315-1325(2011), DOI: [10.1681/ASN.2010101073](https://doi.org/10.1681/ASN.2010101073)
- [32] W. Lin, X. Wu, J. Wen, Y. Fei, J. Wu, X. Li, N. Wang, "Nicotinamide retains Klotho expression and ameliorates rhabdomyolysis-induced acute kidney injury", Nutrition, 91, 111376(2021), DOI: <https://doi.org/10.1016/j.nut.2021.111376>
- [33] Q. Zhou, S. Lin, R. Tang, P. Veeraragoo, W. Peng, R. Wu, "Role of fosinopril and valsartan on klotho gene expression induced by angiotensin II in rat renal tubular epithelial cells", Kidney and Blood Pressure Research, 33(3), 186-192(2010), DOI: <https://doi.org/10.1159/000316703>
- [34] H. Narumiya, S. Sasaki, N. Kuwahara, H. Irie, T. Kusaba, H. Kameyama, H. Matsubara, "HMG-CoA reductase inhibitors up-regulate anti-aging klotho mRNA via RhoA inactivation in IMCD3 cells" Cardiovascular research, 64(2), 331-336(2004), DOI: <https://doi.org/10.1016/j.cardiores.2004.07.011>
- [35] M. Abolghasemi, T. Yousefi, M. Maniati, & D. Quej, "The interplay of Klotho with signaling pathway and microRNAs in cancers", Journal of Cellular Biochemistry, 120(9), 14306-14317(2019), DOI: [10.1002/jcb.29022](https://doi.org/10.1002/jcb.29022)
- [36] J. Karalliedde, G. Maltese, B. Hill, G. Viberti, L. Gnudi, "Effect of renin-angiotensin system blockade on soluble Klotho in patients with type 2 diabetes, systolic hypertension, and albuminuria", Clinical Journal of the American Society of Nephrology, 8(11), 1899-1905(2013), DOI: <https://doi.org/10.2215/cjn.02700313>
- [37] X. Cheng, Q. Zhou, S. Lin, & R. Wu, "Fosinopril and valsartan intervention in gene expression of Klotho, MMP-9, TIMP-1, and PAI-1 in the kidney of spontaneously hypertensive rats", Zhong Nan Da Xue Xue Bao Yi Xue Ban, 35(10), 1048-1056(2010), <https://doi.org/10.3969/j.issn.1672-7347.2010.10.004>
- [38] X. Li & Q. Zhou, "Effect of valsartan on ultrastructure in the brain tissue and expression of Klotho gene in spontaneously hypertensive rats", Zhong nan da xue xue bao. Yi xue ban, Journal of Central South University", Medical Sciences, (2010), DOI: <https://doi.org/10.3969/j.issn.1672-7347.2010.03.011>
- [39] L. J. Chen, M. F. Cheng, P. M. Ku & J. W. Lin, "Rosiglitazone increases cerebral klotho expression to reverse baroreflex in type 1-like diabetic rats", BioMed research international, 2014(1), 309151(2014), DOI: <https://doi.org/10.1155/2014/309151>
- [40] L. Cheng, L. Zhang, J. Yang & L. Hao, "Activation of peroxisome proliferator-activated receptor γ inhibits vascular calcification by upregulating Klotho", Experimental and Therapeutic Medicine, 13(2), 467-474(2017), DOI: <https://doi.org/10.3892/etm.2016.3996>
- [41] M. R. Haussler, S. Livingston, Z. L. Sabir, C. A. Haussler, & P. W. Jurutka, "Vitamin D receptor mediates a myriad of biological actions dependent on its 1, 25-dihydroxyvitamin D ligand: distinct regulatory themes revealed by induction of Klotho and fibroblast growth Factor-23", JBMR plus, 5(1), e10432(2021), DOI: <https://doi.org/10.1002/jbm4.10432>

- [42] M. Kuro-o, "The Klotho proteins in health and disease", *Nature Reviews Nephrology*, 15(1), 27-44(2019), DOI: <https://doi.org/10.1038/s41581-018-0078-3>
- [43] C. Lerch, R. Shroff, M. Wan, L. Rees, H. Aitkenhead, I. Kaplan Bulut, & ESPN CKD-MBD working group Prytula A Bachetta J Haffner D Klaus G Geßner M Schmitt CP Stabouli S Reusz G Verrina E Groothoff J Tondel C Gamero MA Petrosyan E Bakkaloglu SA Dursun I Shroff R., "Effects of nutritional vitamin D supplementation on markers of bone and mineral metabolism in children with chronic kidney disease", *Nephrol Dial Transplant.*, 33(12), 2208-2217(2018), DOI: <https://doi.org/10.1093/ndt/gfy012>
- [44] J. Xue, L. Wang, Z. Sun & C. Xing, "Basic research in diabetic nephropathy health care: A study of the renoprotective mechanism of metformin", *Journal of medical systems*, 43, 1-13(2019), DOI: <https://doi.org/10.1007/s10916-019-1412-4>
- [45] W. Zhou, M. M. Chen, H. L. Liu, Z. L. Si, W. H. Wu, H. Jiang, Z. H. Zhang, "Dihydroartemisinin suppresses renal fibrosis in mice by inhibiting DNA-methyltransferase 1 and increasing Klotho", *Acta pharmacologica sinica*, 43(10), 2609-2623(2022), DOI: <https://doi.org/10.1038/s41401-022-00898-3>
- [46] W. L. Kang & G. S. Xu, "Atrasentan increased the expression of klotho by mediating miR-199b-5p and prevented renal tubular injury in diabetic nephropathy", *scientific reports*, 6(1), 19979(2016), DOI: <https://doi.org/10.1038/srep19979>
- [47] D. Zou, W. Wu, Y. He, S. Ma & J. Gao, "The role of klotho in chronic kidney disease", *BMC nephrology*, 19(1), 285(2018), DOI: <https://doi.org/10.1186/s12882-018-1094-z>
- [48] R. G. Erben, "Physiological actions of fibroblast growth factor-23", *Frontiers in endocrinology*, 9, 267(2018), DOI: <https://doi.org/10.3389/fendo.2018.00267>
- [49] I. Z. Ben-Dov, H. Galitzer, V. Lavi-Moshayoff, R. Goetz, M. Kuro-o, M. Mohammadi, J. Silver, "The parathyroid is a target organ for FGF23 in rats", *The Journal of clinical investigation*, 117(12), 4003-4008(2007), DOI: <https://doi.org/10.1172/JCI32409>
- [50] M. Kuro-o, "Klotho in health and disease", *Current opinion in nephrology and hypertension*, 21(4), 362-368(2012), DOI: <https://doi.org/10.1097/MNH.0b013e32835422ad>
- [51] R. Anour, O. Andrukhova, E. Ritter, U. Zeitz & R. G. Erben, "Klotho lacks a vitamin D independent physiological role in glucose homeostasis, bone turnover, and steady-state PTH secretion in vivo", *PloS one*, 7(2), e31376(2012), DOI: <https://doi.org/10.1371/journal.pone.0031376>
- [52] R. Mathew, M. Pal Bhadra & U. Bhadra, "Insulin/insulin-like growth factor-1 signalling (IIS) based regulation of lifespan across species", *Biogerontology*, 18, 35-53(2017), DOI: <https://doi.org/10.1007/s10522-016-9670-8>
- [53] S. C. Johnson, "Nutrient sensing, signaling and ageing: the role of IGF-1 and mTOR in ageing and age-related disease", *Biochemistry and Cell Biology of Ageing: Part I Biomedical Science-97*, 49-97(2018), DOI: https://doi.org/10.1007/978-981-13-2835-0_3
- [54] P. Kapahi, M. Kaeblerlein & M. Hansen, "Dietary restriction and lifespan: Lessons from invertebrate models", *Ageing research reviews*, 39, 3-14(2017), DOI: <https://doi.org/10.1016/j.arr.2016.12.005>
- [55] H. T. Vo, A. M. Laszczyk & G. D. King, "Klotho, the key to healthy brain aging?", *Brain Plasticity*, 3(2), 183-194(2018), DOI: <https://doi.org/10.3233/BPL-170057>
- [56] B. Xie, J. Zhou, G. Shu, D. C. Liu, J. Zhou, J. Chen & L. Yuan, "Restoration of klotho gene expression induces apoptosis and autophagy in gastric cancer cells: tumor suppressive role of klotho in gastric cancer", *Cancer cell international*, 13, 1-10(2013), DOI: <https://doi.org/10.1186/1475-2867-13-18>
- [57] X. Zhou, Q. Yang, Y. Xie, J. Sun, J. Hu, P. Qiu, S. Wang, "Tetrahydroxystilbene glucoside extends mouse life span via upregulating neural klotho and downregulating neural insulin or insulin-like growth factor 1", *Neurobiology of aging*, 36(3), 1462-1470(2015), DOI: <https://doi.org/10.1016/j.neurobiolaging.2014.11.002>
- [58] M. Yamamoto, J. D. Clark, J. V. Pastor, P. Gurnani, A. Nandi, H. Kurosu, M. Kuro-o, "Regulation of Oxidative Stress by the Anti-ageing Hormone Klotho*", *Journal of Biological Chemistry*, 280(45), 38029-38034(2005), DOI: <https://doi.org/10.1074/jbc.M509039200>
- [59] Y. Lin & Z. Sun, "In vivo pancreatic β -cell-specific expression of antiaging gene Klotho: a novel approach for preserving β -cells in type 2 diabetes", *Diabetes*, 64(4), 1444-1458(2015), DOI: <https://doi.org/10.2337/db14-0632>
- [60] N. Keles, B. Dogan, M. Kalcik, M. Caliskan, N. N. Keles, F. Aksu, A. Oguz, "Is serum Klotho protective against atherosclerosis in patients with type 1 diabetes mellitus?", *Journal of diabetes and its complications*, 30(1), 126-132(2016), DOI: <https://doi.org/10.1016/j.jdiacomp.2015.09.013>
- [61] F. Tarhani, G. Heidari & A. Nezami, "Evaluation of α -klotho level in insulin dependent diabetes mellitus (IDDM) children", *Journal of Pediatric Endocrinology and Metabolism*, 33(6), 761-765(2020), DOI: <https://doi.org/10.1515/jpem-2019-0591>
- [62] N. Fountoulakis, G. Maltese, L. Gnudi & J. Karalliedde, "Reduced levels of anti-ageing hormone klotho predict renal function decline in type 2 diabetes", *The Journal of Clinical Endocrinology & Metabolism*, 103(5), 2026-2032(2018), DOI: <https://doi.org/10.1210/je.2018-00004>
- [63] A. W. Hart, N. Baeza, A. Apelqvist & H. Edlund, "Attenuation of FGF signalling in mouse β -cells leads to diabetes", *Nature*, 408(6814), 864-868(2000), DOI: <https://doi.org/10.1038/35048589>
- [64] Y. Lin & Z. Sun, "Antiaging gene klotho attenuates pancreatic β -cell apoptosis in type 1 diabetes", *Diabetes*, 64(12), 4298-4311(2015), DOI: <https://doi.org/10.2337/db15-0066>
- [65] T. Rubinek, I. Wolf, "The role of alpha-klotho as a universal tumor suppressor", *Vitamins & Hormones*, 101, 197-214(2016), DOI: <https://doi.org/10.1016/bs.vh.2016.03.001>
- [66] M. Abolghasemi, T. Yousefi, M. Maniati, D. Quejueq, "The interplay of Klotho with signaling pathway and microRNAs in cancers", *Journal of Cellular Biochemistry*, 120(9), 14306-14317(2019), DOI: <https://doi.org/10.1002/jcb.29022>
- [67] F. Ewendt, M. Feger & M. Föller, "Role of fibroblast growth factor 23 (FGF23) and α Klotho in cancer", *Frontiers in Cell and Developmental Biology*, 8, (2021), DOI: <https://doi.org/10.3389/fcell.2020.601006>
- [68] L. Abramovitz, T. Rubinek, H. Ligumsky, S. Bose, I. Barshack, C. Avivi, I. Wolf, "KL1 internal repeat mediates klotho tumor suppressor activities and inhibits bFGF and IGF-I signaling in pancreatic cancer", *Clinical Cancer Research*, 17(13), 4254-4266(2011), DOI: <https://doi.org/10.1158/1078-0432.CCR-10-2749>
- [69] B. Sanz, H. Arrieta, C. Rezola-Pardo, A. Fernández-Atutxa, J. Garin-Balerdi, N. Arizaga, J. Irazusta, "Low serum klotho concentration is associated with worse cognition, psychological components of frailty, dependence, and falls in nursing home residents", *Scientific reports*, 11, 9098(2021), DOI: <https://doi.org/10.1038/s41598-021-88455-6>
- [70] M. F. Cheng, L. J. Chen & J. T. Cheng, "Decrease of Klotho in the kidney of streptozotocin-induced diabetic rats", *BioMed Research International*, 2010(1), 513853(2010), DOI: <https://doi.org/10.1155/2010/513853>
- [71] M. C. Hu, M. Kuro-o & O. W. Moe, "Klotho and chronic kidney disease", *Phosphate and Vitamin D in Chronic Kidney Disease*, 180, 47-63(2013), DOI: <https://doi.org/10.1159/000346778>

- [72] G. P. Dias, T. Murphy, D. Stangl, S. Ahmet, B. Morisse, A. Nix, S. ... & Thuret, "Intermittent fasting enhances long-term memory consolidation, adult hippocampal neurogenesis, and expression of longevity gene Klotho", *Molecular psychiatry*, 26(11), 6365-6379(2021), DOI: <https://doi.org/10.1038/s41380-021-01102-4>
- [73] Driscoll, Y. Ma, C. L. Gallagher, S. C. Johnson, S. Asthana, B. P. Hermann, O. C. Okonkwo, "Age-related tau burden and cognitive deficits are attenuated in KLOTHO KL-VS heterozygotes", *Erratum*, (2021), DOI: <https://doi.org/10.3233/JAD-219006>
- [74] M. Laszczyk, S. Fox-Quick, H. T. Vo, D. Nettles, P. C. Pugh, L. Overstreet-Wadiche, G. D. King, "Klotho regulates postnatal neurogenesis and protects against age-related spatial memory loss", *Neurobiology of aging*, 59, 41-54(2017), DOI: <https://doi.org/10.1016/j.neurobiolaging.2017.07.008>
- [75] N. Tasnim, P. Dutta, J. Nayeem, P. Masud, A. Ferdousi, A. S. Ghosh, A. T. Khan, "Osteoporosis, an inevitable circumstance of chronic kidney disease: a systematic review", *Cureus*, 13(10), (2021), DOI: <https://doi.org/10.7759/cureus.18488>
- [76] S. Doi, Y. Zou, O. Togao, J. V. Pastor, G. B. John, L. Wang, M. Kuro-o, "Klotho inhibits transforming growth factor- β 1 (TGF- β 1) signaling and suppresses renal fibrosis and cancer metastasis in mice", *Journal of Biological Chemistry*, 286(10), 8655-8665(2011), DOI: <https://doi.org/10.1074/jbc.M110.174037>
- [77] K. Chen, S. Wang, Q. W. Sun, B. Zhang, M. Ullah & Z. Sun, "Klotho deficiency causes heart aging via impairing the Nrf2-GR pathway", *Circulation research*, 128(4), 492-507(2021), DOI: <https://doi.org/10.1161/CIRCRESAHA.120.317348>
- [78] C. Manrique, J. Habibi, A. R. Aroor, J. R. Sowers, G. Jia, M. R. Hayden, V. G. DeMarco, "Dipeptidyl peptidase-4 inhibition with linagliptin prevents western diet-induced vascular abnormalities in female mice", *Cardiovascular Diabetology*, 15, 1-11(2016), DOI: <https://doi.org/10.1186/s12933-016-0414-5>
- [79] A. Olejnik, A. Franczak, A. Krzywonos-Zawadzka, M. Kałużna-Oleksy & I. Bil-Lula, "The biological role of klotho protein in the development of cardiovascular diseases", *BioMed research international*, 2018(1), 5171945(2018), DOI: <https://doi.org/10.1155/2018/5171945>
- [80] F. Wang & J. Zheng, "Association between serum alpha-Klotho and severe abdominal aortic calcification among civilians in the United States", *Nutrition, Metabolism and Cardiovascular Diseases*, 32(6), 1485-1492(2022), DOI: <https://doi.org/10.1016/j.numecd.2022.02.017>
- [81] Q. Huang, Y. Chen, S. Shen, Y. Wang, L. Liu, S. Wu, J. Wu, "Klotho antagonizes pulmonary fibrosis through suppressing pulmonary fibroblasts activation, migration, and extracellular matrix production: a therapeutic implication for idiopathic pulmonary fibrosis", *Aging (Albany NY)*, 12(7), 5812(2020), DOI: <https://doi.org/10.18632/aging.102978>
- [82] T. Landry, D. Shookster & H. Huang, "Circulating α -klotho regulates metabolism via distinct central and peripheral mechanisms", *Metabolism*, 121, 154819(2021), DOI: <https://doi.org/10.1016/j.metabol.2021.154819>
- [83] Y. Lin & Z. Sun, "Antiaging gene Klotho enhances glucose-induced insulin secretion by up-regulating plasma membrane levels of TRPV2 in MIN6 β -cells", *Endocrinology*, 153(7), 3029-3039(2012), DOI: <https://doi.org/10.1210/en.2012-1091>
- [84] G. J. Prud'homme, Y. Glinka, M. Kurt, W. Liu & Q. Wang, "The anti-aging protein Klotho is induced by GABA therapy and exerts protective and stimulatory effects on pancreatic beta cells", *Biochemical and biophysical research communications*, 493(4), 1542-1547(2017), DOI: <https://doi.org/10.1016/j.bbrc.2017.10.029>
- [85] H. T. Vo, A. M. Laszczyk, & G. D. King, "Klotho, the key to healthy brain aging?", *Brain Plasticity*, 3(2), 183-194(2018), DOI: <https://doi.org/10.3233/BPL-170057>
- [86] K. Hanson, K. Fisher & N. M. Hooper, "Exploiting the neuroprotective effects of α -klotho to tackle ageing-and neurodegeneration-related cognitive dysfunction", *Neuronal signaling*, 5(2), NS20200101(2021), DOI: <https://doi.org/10.1042/NS20200101>
- [87] F. Veronesi, V. Borsari, A. Cherubini & M. Fini, "Association of Klotho with physical performance and frailty in middle-aged and older adults: A systematic review", *Experimental Gerontology*, 154, 111518(2021), DOI: <https://doi.org/10.1016/j.exger.2021.111518>
- [88] T. Y. Fung, A. Iyaswamy, S. G. Sreenivasmurthy, S. Krishnamoorthi, X. J. Guan, Z. Zhu, M. Li, "Klotho an autophagy stimulator as a potential therapeutic target for Alzheimer's disease: A review", *Biomedicines*, 10(3), 705(2022), DOI: <https://doi.org/10.3390/biomedicines10030705>
- [89] R. Senese, F. Cioffi, G. Petito, F. Goglia & A. Lanni, "Thyroid hormone metabolites and analogues", *Endocrine*, 66(1), 105-114(2019), DOI: <https://doi.org/10.1007/s12020-019-02025-5>
- [90] Y. Sun, P. F. Xia, T. I. M. Korevaar, V. Mustieles, Y. Zhang, X. F. Pan, C. Messerlian, "Relationship between blood trihalomethane concentrations and serum thyroid function measures in US adults", *Environmental Science & Technology*, 55(20), 14087-14094(2021), DOI: <https://doi.org/10.1021/acs.est.1c04008>
- [91] P. N. Taylor, D. Albrecht, A. Scholz, G. Gutierrez-Buey, J. H. Lazarus, C. M. Dayan & O. E. Okosieme, "Global epidemiology of hyperthyroidism and hypothyroidism", *Nature Reviews Endocrinology*, 14(5), 301-316(2018), DOI: <https://doi.org/10.1038/nrendo.2018.18>
- [92] M. Babić Leko, N. Pleić, I. Gunjača & T. Zemunik, "Environmental factors that affect parathyroid hormone and calcitonin levels", *International journal of molecular sciences*, 23(1), 44(2021), DOI: <https://doi.org/10.3390/ijms23010044>
- [93] C. L. Meuwese, H. Olauson, A. R. Qureshi, J. Ripsveden, P. Barany, C. Vermeer, P. Stenvinkel, "Associations between thyroid hormones, calcification inhibitor levels and vascular calcification in end-stage renal disease", *PloS one*, 10(7), e0132353(2015), DOI: <https://doi.org/10.1371/journal.pone.0132353>
- [94] I. Mizuno, Y. Takahashi, Y. Okimura, H. Kaji & K. Chihara, "Upregulation of the klotho gene expression by thyroid hormone and during adipose differentiation in 3T3-L1 adipocytes", *Life sciences*, 68(26), 2917-2923(2001), DOI: [https://doi.org/10.1016/S0024-3205\(01\)01092-X](https://doi.org/10.1016/S0024-3205(01)01092-X)
- [95] S. K. Soo, P. D. Rudich, A. Traa, N. Harris-Gauthier, H. J. Shields & J. M. Van Raamsdonk, "Compounds that extend longevity are protective in neurodegenerative diseases and provide a novel treatment strategy for these devastating disorders", *Mechanisms of ageing and development*, 190, 111297(2020), DOI: <https://doi.org/10.1016/j.mad.2020.111297>
- [96] M. R. Haussler, S. Livingston, Z. L. Sabir, C. A. Haussler & P. W. Jurutka, "Vitamin D receptor mediates a myriad of biological actions dependent on its 1", 25-dihydroxyvitamin D ligand: distinct regulatory themes revealed by induction of Klotho and fibroblast growth Factor-23. *JBM plus*, 5(1), e10432, (2021), DOI: <https://doi.org/10.1002/jbm4.10432>
- [97] M. F. Ali, S. K. B. Venkatarayappa, M. Benny, C. Rojas, K. Yousefi, L. A. Shehadeh, K. C. Young, "Effects of Klotho supplementation on hyperoxia-induced renal injury in a rodent model of postnatal nephrogenesis", *Pediatric research*, 88(4), 565-570(2020), DOI: <https://doi.org/10.1038/s41390-020-0803-z>
- [98] T. H. Chen, M. Kuro-o, C. H. Chen, Y. M. Sue, Y. C. Chen, H. H. Wu, & C. Y. Cheng, "The secreted Klotho protein restores phosphate retention and suppresses accelerated aging in Klotho mutant mice", *European journal of pharmacology*(1-3), 67-73(2013), DOI: <https://doi.org/10.1016/j.ejphar.2012.09.032>

- [99] H. J. Oh, B. Y. Nam, M. Wu, S. Kim, J. Park, S. Kang, S. H. Han, "Klotho plays a protective role against glomerular hypertrophy in a cell cycle-dependent manner in diabetic nephropathy", *American Journal of Physiology-Renal Physiology*, 315(4), F791-F805(2018), DOI: <https://doi.org/10.1152/ajprenal.00462.2017>
- [100] Z. Rao, T. Landry, P. Li, W. Bunner, B. T. Laing, Y. Yuan & H. Huang, "Administration of alpha klotho reduces liver and adipose lipid accumulation in obese mice", *Heliyon*, 5(4), (2019), DOI: <https://doi.org/10.1007/s13205-022-03123-4>
- [101] Takenaka, H. Kobori, T. Inoue, T. Miyazaki, H. Suzuki, A. Nishiyama, M. Hayashi, "Klotho supplementation ameliorates blood pressure and renal function in DBA/2-*pcy* mice, a model of polycystic kidney disease", *American Journal of Physiology-Renal Physiology*, 318(3), F557-F564(2020), DOI: <https://doi.org/10.1152/ajprenal.00299.2019>
- [102] T. Arbel Rubinstein, I. Reuveni, A. Hesin, A. Klein-Goldberg, H. Olauson, T. E. Larsson, T. Rubinek, "A transgenic model reveals the role of klotho in pancreatic cancer", (2021), DOI: <https://doi.org/10.3390/cancers13246297>
- [103] Y. J. Shin, K. Luo, Y. Quan, E. J. Ko, B. H. Chung, S. W. Lim & C. W. Yang, "Therapeutic challenge of minicircle vector encoding klotho in animal model", *American Journal of Nephrology*, 49(5), 413-424(2019), DOI: <https://doi.org/10.1159/000499863>
- [104] S. S. Li, A. L. He, Z. Y. Deng & Q. F. Liu, "Ginsenoside-Rg1 protects against renal fibrosis by regulating the Klotho/TGF- β 1/Smad signaling pathway in rats with obstructive nephropathy", *Biological and Pharmaceutical Bulletin*, 41(4), 585-591(2018), DOI: <https://doi.org/10.3389/fphar.2017.00362>
- [105] T. Morishima & E. Ochi, "Impact of a single bout of resistance exercise on serum Klotho in healthy young men", *Physiological Reports*, 9(21), e15087(2021), DOI: <https://doi.org/10.14814/phy2.15087>
- [106] F. J. Amaro-Gahete, A. de-la-O, L. Jurado-Fasoli, J. R. Ruiz, M. J. Castillo & A. Gutiérrez, "Role of exercise on S-Klotho protein regulation: a systematic review", *Current aging science*, 11(2), 100-107(2018), DOI: <https://doi.org/10.2174/1874609811666180702101338>
- [107] T. Arbel Rubinstein, I. Reuveni, A. Hesin, A. Klein-Goldberg, H. Olauson, T. E. Larsson, T. Rubinek, "A transgenic model reveals the role of klotho in pancreatic cancer", *13*(24), 6297(2021), DOI: <https://doi.org/10.3390/cancers13246297>
- [108] Y. J. Shin, K. Luo, Y. Quan, E. J. Ko, B. H. Chung, S. W. Lim & C. W. Yang, "Therapeutic challenge of minicircle vector encoding klotho in animal model", *American Journal of Nephrology*, 49(5), 413-424(2019), DOI: <https://doi.org/10.1159/000499863>
- [109] S. S. Li, A. L. He, Z. Y. Deng & Q. F. Liu, "Ginsenoside-Rg1 protects against renal fibrosis by regulating the Klotho/TGF- β 1/Smad signaling pathway in rats with obstructive nephropathy", *Biological and Pharmaceutical Bulletin*, 41(4), 585-591(2018), DOI: <https://doi.org/10.3389/fphar.2017.00362>
- [110] F. J. Amaro-Gahete, A. de-la-O, L. Jurado-Fasoli, J. R. Ruiz, M. J. Castillo & A. Gutiérrez, "Role of exercise on S-Klotho protein regulation: a systematic review", *Current aging science*, 11(2), 100-107(2018), DOI: <https://doi.org/10.2174/1874609811666180702101338>