

KEY

KLOTHO INTERVENTIONAL STRATEGIE ACTIVE-AGENTS TARGET

REVISED: 8/25/2023

- KIS INCLUDED AGENTS
- Direct Up-Regulated
- Direct Down Regulated
- Combined Antioxidants
- Demethylation Agents

Downstream Signaling (Klotho Activation of Molecular Pathways):

(A) (Klotho) activates (B) (FGF23), which downregulates (C) (PI3K/Akt), affecting (D) (Insulin/IGF-1). (A) (Klotho) upregulates (E) Epigenetic mechanisms that lead to the increase of (F) (Nrf2) and (G) (PPAR-γ). (A) (Klotho) also upregulates (H) (SIRT1) and (I) (AMPK) and modifies (J) (Ion Channels), downregulating (K) (MAPK/ERK). (A) (Klotho) inhibits (L) (mTOR), (M) (NF-Kb), and (N) (Wnt). (A) (Klotho) can increase the activity of (O) Antioxidant pathways, particularly through (F) (Nrf2), which can upregulate cellular (O) Antioxidant responses and decrease oxidative stress.

Upstream Signaling (Molecular Pathway Activation of Klotho):

••(B) (FGF23) stimulates the production of (A) (Klotho). Upregulation of ••(C) (PI3K/Akt), often via stimulation by (D) (Insulin/IGF-1), is associated with enhanced Klotho expression. ••(E) (Epigenetic mechanisms) such as DNA methylation and histone modifications can alter the expression of the Klotho gene, leading to increased production of (A) Klotho. Activation of ••(F) (Nrf2) can increase Klotho gene transcription. ••(G) (PPAR-γ) activation is associated with upregulation of Klotho. Stimulation of ••(H) (SIRT1) or (I) (AMPK) can lead to an increase in Klotho production.

Upstream Signaling (Molecular Pathway Activation of Klotho):

Alterations in ••(J) (Ion Channels) can also stimulate Klotho expression. Downregulation of ••(K) (MAPK/ERK) can lead to upregulation of Klotho. Inhibition of ••(L) (mTOR) or ••(M) (NF-Kb) has been linked with increased Klotho expression. Inhibition of the ••(N) (Wnt) signaling pathway can upregulate Klotho. Activation of (O) Antioxidant pathways, often through ••(F) (Nrf2), particularly under conditions of oxidative stress, can lead to an increase in the expression and activity of (A) Klotho.

The Molecular Pathways Principally Involved in Klotho Regulation are Shown Above

KEY MOL PATHWAYS >>>>		<<<< Upregulating Nrf2 downregulates NF-Kb / Upregulating NF-Kb downregulates Nrf2 >>>>										<<<< Nrf2 Upregulates Antioxidant Pathways >>>>					
KEY		<<<< Signaling Complex >>>>					<<<< SIRT1 & AMPK = Primary Activators of Nrf2 >>>>										
KLOTHO (KAP)		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	
AGENTS		Klotho	FGF23/Klotho	PI3K/Akt	Insulin/IGF	Epigenetics	Nrf2	PPAR-γ	SIRT1	AMPK	Ion Channels	MAPK/Erk	mTOR	NF-Kb	Wnt	Antioxidant	
Desired Agent Modulation Direction		Activated	Activated	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Activated	
Klotho Target Signaling Profile		→	→	←	←	→	→	→	→	→	←	←	←	←	←	→	
AGENTS		Indicates direct up () or down-regulation () of this molecular pathway								Indicates core component of Klotho Protocol (KP)							
1	<input checked="" type="checkbox"/> Curcumin 15 Additive Complementary Synergistic 110	Activated	Modified	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Activated	Modified	Down-Reg	Down-Reg	Down-Reg	Modified	Activated	
		Resveratrol Quercetin Vitamin D	Vitamin D Calcitriol	Berberine Resveratrol GTP-EGCG	Berberine Metformin Resveratrol	Genistein Sulforaphane	Sulforaphane Fibrates Resveratrol	Rosiglitazone Fibrates Thiazolidinediones	Fisetin Resveratrol NR / NMN = NAD	Metformin Berberine Resveratrol	Cal Channel Blik Potassium	Rapamycin Resveratrol Genistein	Rapamycin Resveratrol	Quercetin Resveratrol GTP-EGCG	Quercetin Resveratrol Vitamin D	Glycine, NAC Glutathione Vitamin A	
2	<input checked="" type="checkbox"/> Resveratrol 14 Additive Complementary Synergistic 116	Activated	Activated	Activated	Down-Reg	Activated	Activated	Activated	Activated	Activated	Modulated	Modulated	Down-Reg	Down-Reg	Down-Reg	Activated	
		Curcumin Vitamin D	Vitamin D Calcitriol	Berberine Curcumin	Metformin	Curcumin	Sulforaphane Curcumin	Rosiglitazone Fibrates	Curcumin Fisetin Berberine	Metformin Berberine	TRPV5 agonists	Curcumin GTP-EGCG	Curcumin Rapamycin	Curcumin Quercetin	Curcumin Quercetin	Vitamin C Vitamin E	
	<input checked="" type="checkbox"/> Pterostilbene 14 Additive Complementary Synergistic 0	Activated	Activated	Activated	Down-Reg	Activated	Activated	Activated	Activated	Activated	Modulated	Modulated	Down-Reg	Down-Reg	Down-Reg	Activated	
		Curcumin Resveratrol	Vitamin D Magnesium	Curcumin	Metformin	Curcumin Resveratrol	Curcumin Sulforaphane	Curcumin Resveratrol	Curcumin Resveratrol	Metformin Resveratrol	Calcium Magnesium	Curcumin Resveratrol	Curcumin Resveratrol	Curcumin Resveratrol	Curcumin Resveratrol	Curcumin Resveratrol	
3	<input checked="" type="checkbox"/> Vitamin D 14 Additive Complementary Synergistic 22	Activated	Activated	Activated	Un-Affected	Modulated	Activated	Modulated	Activated	Activated	Modulated	Activated	Down-Reg	Down-Reg	Modulated	Activated	
		Calcium Magnesium Omega-3	Phosphate Iron	Resveratrol	-	Folic Acid Vitamin B12	Resveratrol Curcumin	Omega-3 Thiazolidinediones	Resveratrol NR / NMN = NAD	Metformin AICAR Resveratrol	Calcium Magnesium	EGF PDGF	Rapamycin Resveratrol	Omega-3 Curcumin	Lithium Wnt3a	Vitamin C Vitamin E	
4	<input checked="" type="checkbox"/> GTP-EGCG 13 Green Tea Polyphenols Additive Complementary Synergistic 9	Activated	Activated	Activated	Down-Reg	Activated	Activated	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Un-Affected	Activated	
		Exercise CR	Vitamin D	Metformin Rapamycin	Metformin Rapamycin	Metformin CR GTP-EGCG	Vitamin C Vitamin E	Omega-3	Resveratrol NR / NMN = NAD	Metformin Exercise	Calcium Potassium	-	Rapamycin CR	Omega-3 Curcumin	-	Vitamin C Vitamin E	
	<input checked="" type="checkbox"/> Quercetin 15 Additive Complementary Synergistic 14	Activated	Activated	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Activated	Modulated	Modulated	Down-Reg	Down-Reg	Down-Reg	Activated	
		Resveratrol Curcumin	Resveratrol Vitamin D	Curcumin	Metformin Resveratrol	5-Azacytidine, Valproic acid Garcinol	Resveratrol Sulforaphane	Rosiglitazone Fibrates Thiazolidinediones	Resveratrol Curcumin NR / NMN = NAD	Metformin Resveratrol	TRPV5 agonists Resveratrol	Resveratrol Curcumin PPAR8059 (ERK inhibitor)	Rapamycin Resveratrol	Resveratrol Curcumin	Resveratrol Curcumin	Corticosteroids Vitamin C	

+	Fisetin	14	Activated	Activated	Activated	Modulated	Activated	Activated	Activated	Activated	Modulated	Activated	Down-Reg	Down-Reg	Modulated	Activated	
	Additive Complementary Synergistic	37	Vitamin D Magnesium	Phosphate Vitamin D	Omega-3	Metformin Resveratrol	GTP-EGCG Curcumin	Curcumin Sulforaphane	Pioglitazone Omega-3	Resveratrol NR / NMN = NAD	Metformin Resveratrol	Calcium Potassium	GTP-EGCG Curcumin	Rapamycin Resveratrol	Resveratrol Curcumin	Vitamin D Curcumin	Vitamin E Vitamin C
	+	Genistein	13	Activated	Activated	Activated	Down-Reg	Activated	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Un-Affected	Activated
	Additive Complementary Synergistic	5	Exercise Calorie Restriction	Vitamin D	?	Metformin Rapamycin	Metformin CR	Vitamin C, E	Omega-3	Resveratrol NR / NMN = NAD	Metformin Exercise	Calcium Potassium	-	Rapamycin CR	Omega-3 Curcumin	-	Vitamin C Vitamin E
+	Berberine	15	Activated	Activated	Down-Reg	Modulated	Activated	Activated	Activated	Activated	Modulated	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Activated	
	Additive Complementary Synergistic	0	Vitamin D Curcumin	Vitamin D Calcitriol	Metformin Resveratrol	Metformin Resveratrol	Quercetin Resveratrol	Curcumin Sulforaphane	Omega-3 Pioglitazone	Resveratrol Quercetin	Metformin Exercise	Calcium Magnesium	Curcumin Resveratrol	Rapamycin Resveratrol	Omega-3 Curcumin	Curcumin Resveratrol	Vitamin C Vitamin E Sulforaphane
5	Sodium Butyrate	15	Activated	Activated	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Activated	
	Additive Complementary Synergistic	0	Resveratrol Quercetin Exercise CR	Resveratrol Vitamin D Phosphorus	Resveratrol Curcumin	Metformin Rapamycin	Metformin CR	Resveratrol Sulforaphane Vitamin C Vitamin E	Rosiglitazone Fibrates Omega-3	Resveratrol Curcumin NR / NMN = NAD	Metformin Berberine Exercise	Calcium Potassium	Resveratrol Curcumin	Rapamycin Resveratrol CR	Resveratrol Curcumin Omega-3	Resveratrol Curcumin	Resveratrol Vitamin C Vitamin E
	+	Oleuropein	11	UnKnown	UnKnown	Modulated	Down-Reg	Modulated	Activated	Activated	Activated	UnKnown	Down-Reg	Down-Reg	Down-Reg	UnKnown	Activated
		Additive Complementary Synergistic	0	-	-	Fisetin Curcumin	Metformin Curcumin	Fisetin Curcumin	Fisetin Curcumin	Curcumin Omega-3	Resveratrol Fisetin	Metformin Curcumin	-	Curcumin Fisetin	Curcumin Fisetin	Curcumin Fisetin	-
+	Ursolic Acid	10	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Activated	Activated	Modulated	Activated	Un-Affected	Modulated	Down-Reg	Down-Reg	Activated	
	Additive Complementary Synergistic	0	-	-	Resveratrol Curcumin	Metformin Rapamycin	-	Resveratrol Sulforaphane Vitamin C Vitamin E	Rosiglitazone Fibrates Omega-3	Resveratrol Curcumin NR / NMN = NAD	Metformin Berberine Exercise	-	Resveratrol Curcumin	Rapamycin Resveratrol CR	Resveratrol Curcumin Omega-3	Resveratrol Curcumin	Vitamin C Vitamin E
+	Policosanol	10	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Activated	Activated	Modulated	Activated	Un-Affected	Modulated	Down-Reg	Down-Reg	Activated	
	Additive Complementary Synergistic	0	-	-	Resveratrol Curcumin	Metformin Rapamycin	-	Resveratrol Sulforaphane Vitamin C Vitamin E	Rosiglitazone Fibrates Omega-3	Resveratrol Curcumin NR / NMN = NAD	Metformin Berberine Exercise	-	Resveratrol Curcumin	Rapamycin Resveratrol CR	Resveratrol Curcumin Omega-3	Resveratrol Curcumin	Vitamin C Vitamin E
6	Rapamycin	15	Activated	Activated	Down-Reg	Down-Reg	Modulated	Activated	Activated	Activated	Un-Affected	Un-Affected	Down-Reg	Down-Reg	Modulated	Activated	
	Additive Complementary Synergistic	25	Fisetin Vitamin D	Phosphate Vitamin D	Metformin Fisetin	Metformin Fisetin	Fisetin Curcumin	Fisetin Curcumin	Omega-3 Fisetin	Resveratrol NR / NMN = NAD	Fisetin Metformin	-	-	Fisetin Resveratrol	Fisetin Curcumin	-	Fisetin Vitamin C
	+	Metformin	15	Activated	Un-Affected	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Un-Affected	Un-Affected	Down-Reg	Down-Reg	Un-Affected	Activated
	Additive Complementary Synergistic	46	Exercise CR	-	Insulin	Genistein Rapamycin	Resveratrol CR	Antioxidants Vitamin C Vitamin E	Omega-3	Resveratrol NR / NMN = NAD	Exercise Resveratrol	-	-	Rapamycin CR	Omega-3 Curcumin	-	AntiOxidants Vitamin C Vitamin E
X	Statins	15	Activated	Un-Affected	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Un-Affected	Un-Affected	Down-Reg	Down-Reg	Un-Affected	Activated	
	Additive Complementary Synergistic	46	Exercise CR	-	Insulin	Genistein Rapamycin	Resveratrol CR	Antioxidants Vitamin C Vitamin E	Omega-3	Resveratrol NR / NMN = NAD	Exercise Resveratrol	-	-	Rapamycin CR	Omega-3 Curcumin	-	AntiOxidants Vitamin C Vitamin E
7	Vitamin C	9	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Activated	Modulated	Un-Affected	Activated	Un-Affected	Activated	Modulated	Down-Reg	Un-Affected	Activated
	Additive Complementary Synergistic	26	-	-	Resveratrol Vitamin E	Chromium Omega-3	Folic Acid Vitamin B12	Resveratrol Curcumin	Omega-3 Thiazolidinediones	-	Metformin Resveratrol	-	EGF PDGF	Rapamycin Resveratrol	Omega-3 Curcumin	-	Vitamin E Selenium
8	Vitamin B12	1	Un-Affected	Un-Affected	Un-Affected	Un-Affected	Activated	Un-Affected	Un-Affected	Un-Affected	Un-Affected	Un-Affected	Un-Affected	Un-Affected	Un-Affected	Un-Affected	
	Additive Complementary Synergistic	25	-	-	-	-	SAME Folic Acid	-	-	-	-	-	-	-	-	-	

9	Nicotinamide Mononucleotide	10	13	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Modulated	Modulated	Activated	Activated	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Activated
	Additive Complementary Synergistic			-	-	Resveratrol Curcumin	Berberine, Metformin	Resveratrol Curcumin	Curcumin Sulforaphane,	Berberine, Curcumin	Resveratrol Curcumin	Metformin Resveratrol	-	-	Resveratrol Rapamycin	Curcumin Resveratrol	-	Curcumin Sulforaphane
10	Magnesium	7	8	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Modulated	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Un-Affected	Un-Affected	Un-Affected	Modulated
	Additive Complementary Synergistic			-	-	Vitamin D Omega-3	Chromium Vanadium	-	Vitamin C Vitamin E	-	-	Metformin Resveratrol	Calcium Potassium	Omega-3 Vitamin D	-	-	-	Vitamin C Vitamin E
11	Zinc	8	0	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Modulated	Un-Affected	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Modulated	Un-Affected	Modulated
	Additive Complementary Synergistic			-	-	Resveratrol Quercetin	Chromium Cinnamon	Curcumin GTP-EGCG	Curcumin Quercetin	-	-	-	Calcium Magnesium	Omega-3 Resveratrol	-	Curcumin Omega-3	-	Vitamin C Vitamin E
	Lithium	11	2	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Modulated	Modulated	Modulated	Modulated	Un-Affected
	Additive Complementary Synergistic			-	-	Vitamin D Omega-3	Chromium Vanadium	Curcumin Resveratrol Quercetin Genistein	-	-	Resveratrol Nicotinamide Riboside	Metformin Resveratrol	Calcium Potassium	Omega-3 Vitamin D	Resveratrol Rapamycin	Curcumin Omega-3	Beta-catenin	-
12	Sulforaphane	12	13	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Activated	Activated	Activated	Modulated	Un-Affected	Modulated	Modulated	Down-Reg	Modulated	Activated
	Additive Complementary Synergistic			-	-	Resveratrol Quercetin	Berberine Cinnamon	Curcumin GTP-EGCG	Curcumin Quercetin	Omega-3 Berberine	-	Metformin Resveratrol	-	Omega-3 Resveratrol	Resveratrol Rapamycin	Curcumin Omega-3	Beta-catenin inhibitors	Vitamin C Vitamin E
	Artichoke	11	0	UnKnown	UnKnown	Modulated	Activated	Modulated	Activated	Activated	UnKnown	Activated	Modulated	Modulated	Modulated	Down-Reg	Modulated	Activated
	Additive Complementary Synergistic			-	-	Curcumin Fisetin	Curcumin Fisetin	Curcumin Fisetin	Curcumin Fisetin	Omega-3 Curcumin	-	Metformin Fisetin	Calcium Potassium	Curcumin Fisetin	Curcumin Fisetin	Curcumin Fisetin	Curcumin Fisetin	Vitamin C
13	Omega-3	11	38	Un-Affected	Un-Affected	Modulated	Down-Reg	Modulated	Activated	Activated	Activated	Activated	UnKnown	Modulated	Down-Reg	Down-Reg	UnKnown	Activated
	Additive Complementary Synergistic			-	-	Fisetin Curcumin	Metformin Curcumin	Fisetin Curcumin	Fisetin Curcumin	Omega-3 Curcumin	Resveratrol Fisetin	Curcumin Metformin	-	Fisetin Curcumin	Fisetin Curcumin	Fisetin Curcumin	-	Fisetin Curcumin
14	Astaxanthin	9	0	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Activated	Un-Affected	Modulated	Activated	Un-Affected	Modulated	Modulated	Down-Reg	Un-Affected	Activated
	Additive Complementary Synergistic			-	-	Resveratrol Quercetin	Chromium Cinnamon	-	Resveratrol Curcumin	-	Resveratrol NR / NMN = NAD	Metformin Berberine	-	Curcumin Resveratrol	Metformin Rapamycin	Curcumin GTP-EGCG	-	Vitamin C Vitamin E
15	Alpha-lipoic acid	15	0	Activated	Modulated	Modulated	Modulated	Modulated	Activated	Modulated	Activated	Activated	Modulated	Modulated	Down-Reg	Down-Reg	Modulated	Activated
	Additive Complementary Synergistic			Resveratrol	Vitamin D	Insulin	Metformin	Folate Vitamin B12	Resveratrol Curcumin	Sulforaphane	Resveratrol	Metformin	Magnesium	Curcumin Resveratrol	Metformin Rapamycin	Curcumin	Lithium	Vitamin C Vitamin E