

MP Signaling Dir Key >>>

- Core Klotho Agent
- Direct Up-Regulated
- Direct Down Regulated
- Demethylation Agents

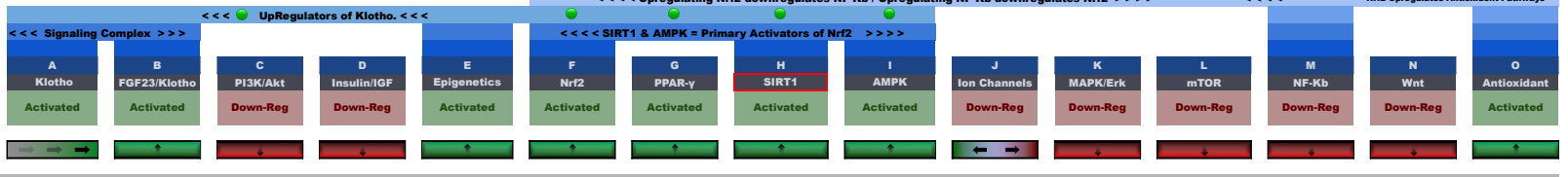
**Forward Signaling (Klotho Activation of Molecular Pathways):**  
 (A) (Klotho) activates (B) (FGF23), which downregulates (C) (PI3K/Akt), affecting (D) (Insulin/IGF-1).  
 (A) (Klotho) upregulates (E) Epigenetic mechanisms that lead to the increase of (F) (Nrf2) and (G) (PPAR-γ).  
 (A) (Klotho) also 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.

**Backward 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.

**Continuation of Backward 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.

KEY MOL PATHWAYS >>>

KEY	
KLOTHO	
AGENTS	15
Desired Agent Modulation Direction	
Klotho's Signaling Pressure	
AGENTS	



1	<input checked="" type="checkbox"/> Curcumin	15	Activated	Modified	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Activated	Activated	Modified	Down-Reg	Down-Reg	Down-Reg	Modified	Activated	Resveratrol	Vitamin D	Berberine	Berberine	Genistein	Sulforaphane	Rosiglitazone	Fisetin	Metformin	Cal Channel Blk	Rapamycin	Rapamycin	Quercetin	Quercetin	Glycine, NAC
	Additive Complementary Synergistic	101																															Glutathione
																																	Vitamin A
																																	Vitamin C
																																	Vitamin E
2	<input checked="" type="checkbox"/> Resveratrol	14	Activated	Activated	Activated	Down-Reg	Activated	Activated	Activated	Activated	Activated	Activated	Modulated	Modulated	Down-Reg	Down-Reg	Down-Reg	Activated	Resveratrol	Vitamin D	Berberine	Metformin	Sulforaphane	Rosiglitazone	Fisetin	Metformin	TRPV5 agonists	Curcumin	Curcumin	Curcumin	Curcumin	Vitamin C	
	Additive Complementary Synergistic	102																															Vitamin E
	<input checked="" type="checkbox"/> Pterostilbene	14	Activated	Activated	Activated	Down-Reg	Activated	Activated	Activated	Activated	Activated	Activated	Modulated	Modulated	Down-Reg	Down-Reg	Down-Reg	Activated	Resveratrol	Vitamin D	Berberine	Metformin	Sulforaphane	Rosiglitazone	Fisetin	Metformin	Calcium	Curcumin	Curcumin	Curcumin	Curcumin	Curcumin	
	Additive Complementary Synergistic	0																															Resveratrol
3	<input checked="" type="checkbox"/> Vitamin D	14	Activated	Activated	Activated	Un-Affected	Modulated	Activated	Modulated	Activated	Activated	Activated	Modulated	Activated	Down-Reg	Down-Reg	Modulated	Activated	Calcium	Phosphate	Resveratrol	-	Folic Acid	Resveratrol	Omega-3	Resveratrol	Calcium	EGF	Rapamycin	Omega-3	Lithium	Vitamin C	
	Additive Complementary Synergistic	21																															Vitamin E
	<input checked="" type="checkbox"/> GTP-EGCG Green Tea Polyphenols	13	Activated	Activated	Activated	Down-Reg	Activated	Activated	Activated	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Un-Affected	Activated	Exercise	Vitamin D	Vitamin D	Metformin	Metformin	Vitamin C	Omega-3	Resveratrol	Calcium	-	Rapamycin	Omega-3	-	Vitamin C	
	Additive Complementary Synergistic	9																															Vitamin E
	<input checked="" type="checkbox"/> Quercetin	15	Activated	Activated	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Activated	Activated	Modulated	Modulated	Down-Reg	Down-Reg	Down-Reg	Activated	Resveratrol	Resveratrol	Resveratrol	Metformin	5-Azacytidine, Valproic acid	Resveratrol	Rosiglitazone	Resveratrol	TRPV5 agonists	Resveratrol	Rapamycin	Resveratrol	Resveratrol	Resveratrol	Resveratrol
	Additive Complementary Synergistic	14																															Vitamin C
	<input checked="" type="checkbox"/> Fisetin	14	Activated	Activated	Activated	Modulated	Activated	Activated	Activated	Activated	Activated	Activated	Modulated	Activated	Down-Reg	Down-Reg	Modulated	Activated	Vitamin D	Phosphate	Omega-3	Metformin	GTP-EGCG	Curcumin	Omega-3	Resveratrol	Calcium	GTP-EGCG	Rapamycin	Resveratrol	Resveratrol	Vitamin D	Vitamin E
	Additive Complementary Synergistic	37																															Vitamin C
	<input checked="" type="checkbox"/> Genistein	13	Activated	Activated	Activated	Down-Reg	Activated	Activated	Activated	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Un-Affected	Activated	Exercise	Vitamin D	?	Metformin	Metformin	Vitamin C, E	Omega-3	Resveratrol	Calcium	-	Rapamycin	Omega-3	-	Vitamin C	
	Additive Complementary Synergistic	4																															Vitamin E
	<input checked="" type="checkbox"/> Berberine	15	Activated	Activated	Down-Reg	Modulated	Activated	Activated	Activated	Activated	Activated	Activated	Modulated	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Activated	Vitamin D	Vitamin D	Metformin	Modulated	Quercetin	Curcumin	Omega-3	Resveratrol	Calcium	Curcumin	Rapamycin	Omega-3	Curcumin	Curcumin	Vitamin C
	Additive Complementary Synergistic	0																															Vitamin E
																																	Sulforaphane
5	<input checked="" type="checkbox"/> Sodium Butyrate	15	Activated	Activated	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Activated	Resveratrol	Resveratrol	Resveratrol	Metformin	Metformin	Resveratrol	Rosiglitazone	Resveratrol	Metformin	Calcium	Resveratrol	Rapamycin	Resveratrol	Resveratrol	Resveratrol

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- Demethylation Agents

**Forward Signaling (Klotho Activation of Molecular Pathways):**  
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 (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.

**Backward 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.  
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 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.

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 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.

KEY MOL PATHWAYS >>>

KEY	AGENTS	Desired Agent Modulation Direction	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O		
KLOTHO	15	→	Activated	Activated	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Activated		
			Quercetin	Vitamin D	Curcumin	Rapamycin	CR	Sulforaphane	Fibrates	Curcumin	Berberine	Potassium	Curcumin	Resveratrol	Curcumin	Curcumin	Curcumin	Vitamin C	
			Exercise	Phosphorus	-	-	-	Vitamin C	Omega-3	NR / NMN = NAD	Exercise	-	Fisetin	CR	Omega-3	-	-	Vitamin E	
Oleuropein	11	→	UnKnown	UnKnown	Modulated	Down-Reg	Modulated	Activated	Activated	Activated	Activated	UnKnown	Down-Reg	Down-Reg	Down-Reg	UnKnown	Activated		
			-	-	Fisetin	Metformin	Fisetin	Fisetin	Curcumin	Curcumin	Resveratrol	Metformin	-	Curcumin	Fisetin	Curcumin	Curcumin	-	Curcumin
			-	-	Curcumin	Curcumin	Curcumin	Curcumin	Curcumin	Omega-3	Fisetin	Curcumin	-	Fisetin	Fisetin	Fisetin	-	Fisetin	
Ursolic Acid	10	→	Un-Affected	Un-Affected	Modulated	Down-Reg	Un-Affected	Activated	Activated	Modulated	Activated	Un-Affected	Modulated	Down-Reg	Down-Reg	Un-Affected	Activated		
			-	-	Resveratrol	Metformin	-	Resveratrol	Rosiglitazone	Resveratrol	Metformin	-	Resveratrol	Resveratrol	Curcumin	Resveratrol	Curcumin	Curcumin	Vitamin C
			-	-	Curcumin	Rapamycin	-	Sulforaphane	Fibrates	Curcumin	Berberine	-	Curcumin	Resveratrol	Resveratrol	Curcumin	Curcumin	Curcumin	Vitamin E
6	15	→	Activated	Activated	Down-Reg	Down-Reg	Modulated	Activated	Activated	Activated	Un-Affected	Un-Affected	Down-Reg	Down-Reg	Modulated	Activated			
			Fisetin	Phosphate	Metformin	Metformin	Fisetin	Fisetin	Omega-3	Resveratrol	Fisetin	Un-Affected	-	Fisetin	Resveratrol	Curcumin	Curcumin	Fisetin	
			Vitamin D	Vitamin D	Fisetin	Fisetin	Curcumin	Curcumin	Fisetin	NR / NMN = NAD	Metformin	-	Resveratrol	Curcumin	Curcumin	Curcumin	-	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			
			Exercise	-	Insulin	Genistein	Resveratrol	Antioxidants	Omega-3	Resveratrol	Exercise	-	-	Rapamycin	Omega-3	-	AntiOxidants		
			CR	-	Rapamycin	Rapamycin	CR	Vitamin C	Omega-3	Resveratrol	Resveratrol	-	CR	Curcumin	Curcumin	-	Vitamin C		
7	9	→	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Activated	Modulated	Un-Affected	Activated	Un-Affected	Activated	Modulated	Down-Reg	Un-Affected	Activated		
			-	-	Resveratrol	Chromium	Folic Acid	Resveratrol	Omega-3	-	Metformin	-	EGF	Rapamycin	Omega-3	Curcumin	-	Vitamin E	
			-	-	Vitamin E	Omega-3	Vitamin B12	Curcumin	Thiazolidinediones	Resveratrol	Resveratrol	-	PDGF	Resveratrol	Curcumin	-	-	Selenium	
8	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	Un-Affected		
			-	-	-	-	SAME	-	-	-	-	-	-	-	-	-	-	-	
			-	-	-	-	Folic Acid	-	-	-	-	-	-	-	-	-	-	-	
9	10	→	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Modulated	Modulated	Activated	Activated	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Activated		
			-	-	Resveratrol	Berberine	Resveratrol	Curcumin	Berberine	Resveratrol	Curcumin	Curcumin	-	-	Resveratrol	Curcumin	-	Curcumin	
			-	-	Curcumin	Metformin	Curcumin	Sulforaphane	Curcumin	Curcumin	Metformin	Resveratrol	-	-	Rapamycin	Resveratrol	-	Sulforaphane	
10	7	→	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Modulated	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Un-Affected	Un-Affected	Un-Affected	Modulated		
			-	-	Vitamin D	Chromium	-	Vitamin C	-	-	Metformin	Calcium	Omega-3	-	-	-	-	Vitamin C	
			-	-	Omega-3	Vanadium	-	Vitamin E	-	-	Resveratrol	Potassium	Vitamin D	-	-	-	-	Vitamin E	
11	8	→	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Modulated	Un-Affected	Un-Affected	Un-Affected	Modulated	Modulated	Un-Affected	Modulated	Un-Affected	Modulated		
			-	-	Resveratrol	Chromium	Curcumin	Curcumin	-	-	-	Calcium	Omega-3	-	Curcumin	Curcumin	-	Vitamin C	
			-	-	Quercetin	Cinnamon	GTP-EGCG	Quercetin	-	-	-	Magnesium	Resveratrol	-	Omega-3	Omega-3	-	Vitamin E	
Lithium	14	→	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Un-Affected	Un-Affected	Modulated	Modulated	Modulated	Modulated	Modulated	Modulated	Modulated	Un-Affected		
			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

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KEY MOL PATHWAYS >>>

KEY	
KLOTHO	AGENTS
Desired Agent Modulation Direction	15
Lithium	11
Additive Complementary Synergistic	1
<hr/>	
12	Sulforaphane 12
Additive Complementary Synergistic	11
Artichoke	11
Additive Complementary Synergistic	0
<hr/>	
13	Omega-3 11
Additive Complementary Synergistic	34
<hr/>	
14	Astaxanthin 9
Additive Complementary Synergistic	0

<<< Signaling Complex >>>															<<< UpRegulators of Klotho. <<<					<<< SIRT1 & AMPK = Primary Activators of Nrf2 >>>					<<< Upregulating Nrf2 downregulates NF-Kb / Upregulating NF-Kb downregulates Nrf2 >>>					<<< Nrf2 Upregulates Antioxidant Pathways >>>																																																											
A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O															
Klotho	FGF23/Klotho	PI3K/Akt	Insulin/IGF	Epigenetics	Nrf2	PPAR-γ	SIRT1	AMPK	Ion Channels	MAPK/Erk	mTOR	NF-Kb	Wnt	Antioxidant	Klotho	FGF23/Klotho	PI3K/Akt	Insulin/IGF	Epigenetics	Nrf2	PPAR-γ	SIRT1	AMPK	Ion Channels	MAPK/Erk	mTOR	NF-Kb	Wnt	Antioxidant	Klotho	FGF23/Klotho	PI3K/Akt	Insulin/IGF	Epigenetics	Nrf2	PPAR-γ	SIRT1	AMPK	Ion Channels	MAPK/Erk	mTOR	NF-Kb	Wnt	Antioxidant	Klotho	FGF23/Klotho	PI3K/Akt	Insulin/IGF	Epigenetics	Nrf2	PPAR-γ	SIRT1	AMPK	Ion Channels	MAPK/Erk	mTOR	NF-Kb	Wnt	Antioxidant	Klotho	FGF23/Klotho	PI3K/Akt	Insulin/IGF	Epigenetics	Nrf2	PPAR-γ	SIRT1	AMPK	Ion Channels	MAPK/Erk	mTOR	NF-Kb	Wnt	Antioxidant															
Activated	Activated	Down-Reg	Down-Reg	Activated	Activated	Activated	Activated	Activated	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Down-Reg	Activated	-	-	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	-	-	-	Modulated Resveratrol Quercetin	Modulated Berberine Cinnamon	Modulated Curcumin Resveratrol Quercetin GTP-EGCG	Activated Curcumin Quercetin	Activated Omega-3 Berberine	Activated Resveratrol Nicotinamide Riboside	Modulated Metformin Resveratrol	Un-Affected -	Modulated Omega-3 Resveratrol	Modulated Resveratrol Rapamycin	Down-Reg Curcumin Omega-3	Modulated Beta-catenin inhibitors	Activated Vitamin C Vitamin E	UnKnown	UnKnown	Modulated Curcumin Fisetin	Activated Curcumin Fisetin	Modulated Curcumin Fisetin	Activated Curcumin Fisetin	Activated Omega-3 Curcumin	UnKnown	Activated Metformin Fisetin	Modulated Calcium Potassium	Modulated Curcumin Fisetin	Modulated Curcumin Fisetin	Down-Reg Curcumin Fisetin	Modulated Curcumin Fisetin	Activated Vitamin C	Un-Affected	Un-Affected	Modulated Fisetin Curcumin	Down-Reg Metformin Curcumin	Modulated Fisetin Curcumin	Activated Fisetin Curcumin	Activated Omega-3 Curcumin	Activated Resveratrol Fisetin	Activated Curcumin Metformin	UnKnown -	Modulated Fisetin Curcumin	Down-Reg Fisetin Curcumin	Down-Reg Fisetin Curcumin	UnKnown -	Activated Fisetin Curcumin	Un-Affected	Un-Affected	Modulated Resveratrol Quercetin	Modulated Chromium Cinnamon	Un-Affected -	Activated Resveratrol Curcumin	Un-Affected -	Modulated Resveratrol NR / NMN = NAD	Activated Metformin Berberine	Un-Affected -	Modulated Curcumin Resveratrol	Modulated Metformin Rapamycin	Down-Reg Curcumin GTP-EGCG	Un-Affected -	Activated Vitamin C Vitamin E