Table S1. Known anti-aging compounds, their abilities to increase life span in different organisms (under caloric or dietary restriction [CR or DR, respectively], on a standard diet or fed a high-calorie diet), and the mechanisms of their anti-aging action.

Compound	Increases life span*		Mechanism
	CR/DR	Standard or high-calorie diet	
Caffeine	NT	+ (yeast, CLS) [1]	By inhibiting TORC1, modulates unspecified longevity-related processes [1] governed by the TOR pathway [2,3]
Li^+	+ (nematodes**) [4]	+ (nematodes) [4]	By altering transcription of genes involved in histone methylation, nucleosome composition and chromatin structure, modulates unspecified longevity-related processes [4] known to be influenced by age-related chromatin reorganization [5]
Lipoic acid, propyl gallate, trolox and taxifolin	NT	+ (nematodes [6] (all); fruit flies [7] (lipoic acid))	Antioxidants that may increase life span by detoxifying free radicals and/or enhancing resistance to age-related oxidative stress [6,7]
Metformin, buformin and phenformin	- (nematodes**) [8]	+ (nematodes [8]; mice [9])	Type 2 diabetes therapeutics that - by activating LKB1/AMPK signaling and thereby inhibiting TORC1 [10,11] - modulate unspecified longevity-related processes [8,9] known to be governed by the TOR pathway [2,3,11]
Methionine sulfoximine	NT	+ (yeast, CLS) [12]	By inhibiting glutamine synthetase and reducing both intracellular glutamine level and TORC1-signaling [13], increases life span - perhaps by activating gluconeogenesis and enhancing stress resistance [12]
Mianserin	- (nematodes) [14]	+ (nematodes) [14]	A serotonin receptor antagonist used as an antidepressant in humans; may increase life span by inhibiting neurotransmission related to food sensing, thereby mimicking a DR-like physiological state [14]***
Rapamycin	+ (fruit flies) [16]	+ (yeast, CLS [1,12,17] and RLS [18]; fruit flies [16]; mice [19]; rodent fibroblasts,	By inhibiting TORC1 (yeast and fruit flies) [1,16,17,21] and mTORC1 (mammals)

		human epithelium and fibrosarcoma cells - all RLS [20])	[11,19,21], increases life span by activating macroautophagy (yeast and fruit flies) [16,22] and inhibiting cap-dependent protein translation (fruit flies and mice) [16,19] as well as - perhaps - by promoting gluconeogenesis (yeast) [12], enhancing stress resistance (yeast) [12,18], and increasing neutral lipid levels (fruit flies) [16]
Resveratrol	- (yeast, RLS [23]; fruit flies [24]; mice [25])	+ (yeast, RLS [23] but not CLS [23]; nematodes [24]; fruit flies [24]; fishes [26]; mice [25,28]; human fibroblasts, RLS [27])****	Increases life span by modulating a number of longevity-related processes (*e.g.*, by altering transcription of numerous genes involved in key longevity pathways, stimulating p53 deacetylation, increasing insulin sensitivity and mitochondrial number, reducing IGF-1 levels, activating AMPK and PGC-1α, promoting ER stress response, repressing transcription of PPAR-γ, inhibiting adipocyte differentiation, accelerating storage fat mobilization, inhibiting mTORC1, and activating autophagy [23,25,27-35); its life-extending ability in yeast, nematodes and fruit flies depends on Sir2p - a member of the conserved sirtuin family of NAD^+-dependent protein deacetylases/mono-ADP-ribosyltransferases [23,24,29]*****
SkQ1	NT	+ (fungi, daphnias, fruit flies, mice) [43]	By being specifically targeted to mitochondria, acts as an antioxidant that may increase life span by preventing oxidative damage to proteins and lipids (*i.e.*, cardiolipin), altering mitochondrial morphology, reducing hydrogen peroxide-induced apoptosis and necrosis, and/or slowing down the age-related phosphorylation of histone H2AX [43]
Sodium nitroprusside	NT	+ (human PBMC,RLS) [44]	By activating expression of the human sirtuin SIRT1 and thereby increasing the extent

			of SIRT1-dependent histone H4 lysine 16 deacetylation, may cause the development of an anti-aging pattern of transcription of numerous genes involved in longevity regulation [44]
Spermidine	NT	+ (yeast, CLS; nematodes; fruit flies; human PBMC, RLS) [45]	By inhibiting histone acetyltransferases and promoting histone H3 deacetylation, increases life span by activating transcription of numerous autophagy-related genes; the resulting induction of autophagy suppresses age-related necrotic cell death [45]
Valproic acid	NT	+ (nematodes) [46]	Is used as a mood stabilizer and an anticonvulsant in humans; may increase life span by promoting nuclear localization of the DAF-16 forkhead transcription factor, thereby reducing the pro-aging effect of the insulin/IGF-1 signaling pathway [46]
LY294002	NT	+ (human fibrosarcoma cells, RLS) [47]	An inhibitor of phosphatidylinositol-3-kinase that – by reducing mTORC1 signaling [2,3] – modulates unspecified longevity-related processes [47] known to be governed by the TOR pathway [2,3,11]
U0126	NT	+ (human fibrosarcoma cells, RLS) [47]	An inhibitor of the protein kinase MEK that – by reducing mTORC1 signaling [2,3] – modulates unspecified longevity-related processes [47] known to be governed by the TOR pathway [2,3,11]

[*] Mean, median and/or maximum life spans.

[**] Nematodes carrying mutations that mimic DR under non-DR conditions [4,8].

[***] The ability of mianserin to increase nematode life span can only be seen in liquid media [14], whereas in solid media the compound reduces life span [15].

[****] Increases the replicative life span of yeast grown under non-CR conditions [23] only in one out of four different yeast strain backgrounds [36]; one group has been unable to reproduce the life span extension by resveratrol in nematodes and fruit flies [37]; increases the life of mice only if fed a high-calorie diet, but not a standard diet [25,28].

[*****] Although the life-extending ability of resveratrol in yeast, nematodes and fruit flies depends on Sir2p [23,24,29], it is currently debated whether this anti-aging compound binds to Sir2p (or SIRT1, a mammalian sirtuin) in vivo and/or activates Sir2p or SIRT1 in living cells [30,36-40]; importantly, resveratrol has been shown to inhibit or activate many proteins other than sirtuins by interacting with them [41,42].

Abbreviations: AMPK, the AMP-activated serine/threonine protein kinase; CLS, chronological life span; IGF-1, insulin-like growth factor 1; LKB1, a serine/threonine protein kinase that phosphorylates and activates AMPK; mTORC1, the mammalian target of rapamycin complex 1; NT, not tested; PBMC, peripheral blood mononuclear cells; PGC-1α, peroxisome proliferator-activated receptor-γ co-activator 1α; RLS, replicative life span; TORC1, the yeast target of rapamycin complex 1.

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