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The road ahead for health and lifespan interventions

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Abstract

Aging is a modifiable risk factor for most chronic diseases and an inevitable process in humans. The development of pharmacological interventions aimed at delaying or preventing the onset of chronic conditions and other age-related diseases has been at the forefront of the aging field. Preclinical findings have demonstrated that species, sex and strain confer significant heterogeneity on reaching the desired health- and lifespan-promoting pharmacological responses in model organisms. Translating the safety and efficacy of these interventions to humans and the lack of reliable biomarkers that serve as predictors of health outcomes remain a challenge. Here, we will survey current pharmacological interventions that promote lifespan extension and/or increased healthspan in animals and humans, and review the various anti-aging interventions selected for inclusion in the NIA's Interventions Testing Program as well as the ClinicalTrials.gov database that target aging or age-related diseases in humans.

Keywords

Lifespan; Healthspan; Aging; "anti-aging"; Longevity; Frailty; Translation

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Author's contributions

All the authors were involved in the manuscript conception and design. MGF, ADR and DH wrote the paper, which was revised by MB, RdC and LF. MGF, ADR, MB and JMR prepared the figures and tables. All the authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest, financial or otherwise.

Appendix A. Supplementary data

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1. Introduction

Aging has been recognized as a risk factor for most chronic diseases. It is an inevitable progression towards dysfunction and ultimately death across most living organisms, especially mammals. With aging, there is accumulation of damage that leads to an increase in disease vulnerability and death. However, despite years of intense research, the exact underlying mechanisms that govern aging processes remain poorly understood. Why and how we age still remains a mystery.

Most chronic diseases are multifactorial, polygenic and their clinical manifestations tend to emerge late in life (Fabbri et al., 2015; Ferrucci et al., 2018). The recent increase in life expectancy and the decline in birthrates account for the sharp rise in the number and proportion of older adults around the globe. In 2014, people 65 and older represented 14.5 % of the population, but by 2060, the number of elderly persons will double and outpace the number of children under age 5 (World Health Organization, 2015), which will cause a significant burden of age-related diseases on the economy in both developed and developing countries. This demographic change is already having an impact in individual healthcare costs, which will soon surpass 400$ billion dollars per year in the U.S. alone. In order to contain the escalating increase in health care spending, we must reduce the overall burden of disability and chronic disease.

Aging has long been considered a stochastic, inevitable process towards dyfunction and ultimately death (Hayflick, 2000). However, recent advances in the field of gerontology are showing that there are deterministic mechanisms that might be driving aging with some people aging at a slower rate than others. Therefore, aging should be viewed as adaptive and amenable to interventions aimed at extending health span and life span. Individuals with exceptional longevity often have delayed onset of age-related diseases and disabilities (Evert et al., 2003; Lipton et al., 2010), with a compression of morbidity and increased lifespan, living longer and healthier lives. Exceptional longevity and successful aging are only 20 % heritable (Murabito et al., 2012), while some of the main age-related chronic diseases, such as cancer (~33 %) (Mucci et al., 2016), cardiovascular diseases (~25–35 %) (Gluckman et al., 2016), dementia (i.e: Alzheimer's Disease ~70–79 %) (Selkoe, 1996; Barber, 2012) and others, are highly heritable (Zenin et al., 2019). External factors including environment, psychosocial impact, nutrition, and physical fitness all contribute to deterministic mechanisms of slower/faster aging (Shiels et al., 2019). As we age, our diminished ability to respond to stress renders us more susceptible to adverse health outcomes, leading to declining health and ultimately death. Rockwood and Mitnitski (2011) proposed that this increase in deficit accumulation could represent another way to define frailty.

Ferrucci and colleagues clustered the systemic consequences of the aging process into four main domains (Ferrucci et al., 2010): i) Body composition; ii) balance between energy availability and energy demand; iii) homeostatic dysregulation; and iv) neurodegeneration. Changes in these four domains of the aging phenotypes increase the susceptibility to diseases and reduce the resilience or functional reserve capacity, leading to a condition that is known as frailty and the development of the so-called "geriatric syndromes" (Ferrucci and Studenski, 2012). These syndromes, which include delirium, cognitive impairment, falls,

muscle atrophy (e.g. sarcopenia) and disability, are multifactorial and involve systemic changes in many parts of the body with adverse association of comorbidity with mortality. Some of the interventions presented herein target these four domains.

Recently, the landmark review by López-Otín helped conceptualize the hallmarks of aging by grouping of age-associated cellular and molecular mechanisms into three major categories known as ‘primary’, ‘antagonistic’, and ‘integrative’ hallmarks (Lopez-Otin et al., 2013) (Fig. 1). Genomic instability, telomere attrition, epigenetic alteration, and loss of proteostasis are deemed as primary hallmarks, causally related to molecular damage during aging. Antagonistic hallmarks have a beneficial hormetic function and protective role when expressed at low levels, but detrimental effects might occur at high levels. These hallmarks include deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence. Lastly, stem cell exhaustion and altered intercellular communication, known as integrative hallmarks, are indicators of impaired processes at the molecular and cellular levels, and both indicate a loss of reserve capacity or resilience, ultimately producing the aging phenotypes described by Ferrucci et al. (2010) (Fig. 1). The integration of all these hierarchical levels has been defined as metrics of aging (Ferrucci et al., 2018). Therefore, the geriatric syndromes would be considered ‘phenotypic aging’, and the hallmarks of aging should be viewed as ‘biological aging’. Ultimately a desequilibrum in both levels will lead to changes in cognition and physical performance, known as ‘functional aging’, ending in frailty and a loss of resilience.

In the last two decades, major scientific advances in our understanding of aging processes were achieved in model organisms, which led to the discovery of conserved longevity pathways, as well as the development of genetic, nutritional, and pharmacological interventions that target them. It is likely that the same interventions may provide benefits only in select tissues, organisms, or individuals based on age, sex, and ethnicity (Bartke et al., 2019). In model organisms, lifespan extension is often accompanied by a reduction or delay in morbidity (Fontana et al., 2010). Many of the pro-longevity pathways are also implicated in tissue development and metabolic regulation, as restriction in calorie intake is considered a key modulator in the aging process (de Cabo et al., 2014; Mercken et al., 2012). Drugs that mimic the effects of calorie restriction (CR) have shown life- and healthspan-extending properties through modulation of nutrient-sensing pathways, mitochondrial stress and antioxidant responses, and chromatin silencing (de Cabo et al., 2014; Lopez-Otin et al., 2016).

One of the most active areas of research in aging focuses on the identification of novel pathways that regulate the underlying processes of aging in order to develop interventions aimed at delaying the onset and progression of chronic diseases, preservation of functional capacity, and postponing death. We surmise that increases in mean lifespan with compression of morbidity is an ambitious, yet achievable goal within our reach (Fries et al., 2011; Ebeling et al., 2018), although translation of the advances made from model organisms to human clinical trials still remains a major challenge (Campisi et al., 2019). Nevertheless, there are multiple questions that persist on how to reverse or delay the dysregulation of biological systems that are implicated in age-associated phenotypic changes that lead to frailty and death. In this review, we considered pharmacological interventions

that lead to lifespan extension and/or increase or preservation of function in mammals and human by targeting the hallmarks of aging.

2. Interventions that delay aging

Several small molecules and dietary manipulations based on CR have been developed during the last two decades that target processes of aging. A number of compounds have been found to delay the onset of age-related diseases and increase healthspan and lifespan from yeast to mammals, including nonhuman primates (Fontana et al., 2010; Ravussin et al., 2015; Mattison et al., 2017). These interventions target major signaling pathways whose dysregulation contributes to the emergence of aging phenotypes and disease. These compounds are generally considered CR mimetics that extend lifespan through an improvement of metabolic function, especially via mitochondrial metabolic reprogramming, and include drugs that target i) various growth factor signaling pathways; ii) insulin signaling pathway implicated in carbohydrate and fat metabolism; iii) NAD^+-dependent sirtuins; iv) amino acid pathway; v) autophagy; vi) senescence; and vii) stem cells and rejuvenation factors. There are excellent recent reviews that have extensively covered the benefits of these CR-mimetic compounds and interventions (Fontana et al., 2010; Longo et al., 2015; Rizza et al., 2014; Fontana et al., 2012; Fontana and Partridge, 2015; de Cabo et al., 2014; Martin-Montalvo and de Cabo, 2013; Baur et al., 2012; Novelle et al., 2015; Pan and Finkel, 2017; Custodero et al., 2018; Gurau et al., 2018). Here, we present a brief overview of the beneficial effects that these drugs and interventions confer on the different hallmarks of aging.

2.1. Drugs targeting growth factor pathways

2.1.1. mTOR inhibitors, rapamycin, rapalogs and other—Rapamycin is an antifungal antibiotic that was first isolated from an Easter Island soil sample by Chang et al. (1991). Rapamycin has been approved by FDA for its immunosuppressive and anti-rejection properties (Camardo, 2003). Novel mTOR inhibitors, known as rapalogues, have the same molecular scaffold as rapamycin, but with different physiochemical properties (Lamming and Sabatini, 2013). The anti-cancer properties of rapamycin are associated with inhibition of the mammalian target of rapamycin (mTOR) through interaction with immunophilin FKBP12, which binds next to the kinase region of TOR, a serine/threonine kinase that is regulated by nutrients, growth factors, and the cellular energy status. TOR signals through two multiprotein complexes, termed mTORC1 and mTORC2, with distinct biological outcomes. Acute and chronic exposure to rapamycin has been shown to inhibit mTORC1 whereas inhibition of mTORC2 requires long-term treatment with the drug (for review, see Li et al., 2014). The pro-longevity effects of rapamycin are conveyed through mTORC1 whereas mTORC2 inactivation is believed to be responsible of the insulin resistance phenotype associated with rapamycin treatment (Saxton and Sabatini, 2017).

mTOR is considered a “metabolic master regulator” through its ability to regulate metabolism across metabolically active tissues, such as skeletal muscle, adipose tissue, liver and brain (Sengupta et al., 2010; Tsai et al., 2015; Lamming and Sabatini, 2013; Garelick and Kennedy, 2011). Inhibition of mTORC signaling can also have protective effects during

obesity and type 2 diabetes (Reifsnyder et al., 2018). The healthspan and lifespan extension properties of rapalogs stem from the lowering in mTOR signaling pathway activation triggered by insulin/IGF-1 axis, amino acids and glucose levels, all of which acting in concert to influence the cellular energy status (for review see Kennedy and Lamming, 2016). Pharmacological inhibition of TOR with rapamycin or other mTOR inhibitors promotes lifespan extension in yeast, worm, flies, and mice (Vellai et al., 2003; Cao et al., 2010; Robida-Stubbs et al., 2012), notably by impacting downstream mTORC1-regulated processes that include autophagy, lipid synthesis, mitochondrial metabolism, ribosomal biogenesis, and modulation of the senescence-associated secretory phenotype among others (Pan and Finkel, 2017). The pro-longevity effects of rapamycin are seen preferentially in females than males (Miller et al., 2014). Recently, it has been suggested that the effects of mTORC1 inhibitors, such as the rapalog RAD001, could be mediated by regulation of c-Myc protein, with subsequent reduction in nephropathy lesions found in aged rats (Shavlakadze et al., 2018).

2.2. Drugs targeting insulin signaling pathways, carbohydrates and fat metabolism

2.2.1. Metformin—Metformin (*N,N*-dimethylbiguanide) belongs to the biguanide class of anti-diabetic drugs and is well tolerated compared to other drugs. Metformin is most commonly used as a first-line medication for type 2 diabetes by lowering hepatic glucose production and insulin resistance. The underlying mechanisms by which metformin inhibits hepatic gluconeogenesis remains unknown, although recent studies have shown that metformin could suppress gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase (Madiraju et al., 2014) and by activation of a duodenal pathway dependent on AMP-activated protein kinase (AMPK) (Duca et al., 2015). One of the major clinical advantages of metformin is that it does not induce hypoglycemia or weight gain while correcting hyperglycemia and conferring CR-like benefits such as improvement in insulin sensitivity and AMPK activity and better antioxidant protection. The ability of metformin at improving healthspan and lifespan of drosophila, C. elegans and mice raises the possibility of metformin-based interventions to promote healthy aging in humans (Slack et al., 2012; Cabreiro et al., 2013; Martin-Montalvo et al., 2013; Novelle et al., 2016; Alfaras et al., 2017). Metformin has been reported to abrogate DICER1-mediated cellular senescence by altering microRNA expression (Noren Hooten et al., 2016) and producing epigenetic modifications that regulate the expression levels of several microRNAs to confer protection against diabetes and cancer (Bridgeman et al., 2018). A 6-week treatment with metformin regulates several cellular processes (e.g., DNA repair) and metabolic pathways that include pyruvate metabolism, PPAR and SREBP signaling, and mitochondrial fatty oxidation in skeletal muscle and subcutaneous adipose tissue of older adults (Kulkarni et al., 2018). While neonatal exposure to metformin appears to slow aging down and prolongs lifespan in male mice (Anisimov et al., 2015), administration of the biguanide every other week when initiated in late-life leads to an overall improvement on health without an extension in lifespan as compared to control mice (Alfaras et al., 2017). Long-term metformin treatment has been found to lower the expression of the antioxidant regulator Nrf2 (*Nfe2l2*) and that of neurotrophic factors in the brain of old mice (Allard et al., 2016).

Based on experimental evidences from cellular and animal studies, a recent clinical trial known as TAME (**T**argeting **A**ging with **Me**tformin) will assess whether metformin can delay the onset and/or progression of age-related diseases beyond its effects on glucose metabolism. TAME plans to enroll 3000 subjects, ages 65–79, in 14 different centers across the U.S. (Barzilai et al., 2016). Intriguingly, recent studies have found that the combination of metformin with exercise opposes the exercise-induced benefits in insulin sensitivity, cardiorespiratory fitness, and mitochondrial adaptations to aerobic exercise in older adults (Malin et al., 2012; Konopka et al., 2019).

2.2.2. 17α -Estradiol—While the feminizing hormone 17β-estradiol (17β-E2) is the most biologically active and abundant estrogen in circulation, 17α-estradiol (17α-E2) is considered a non-feminizing hormone with reduced affinity for the estrogen receptor. Previous studies have shown that 17α-E2 can confer protection against oxidative stress and age-related degenerative brain disorders, such as Parkinson's and Alzheimer's diseases, and age related inflammation (Dykens et al., 2005; Santos et al., 2017). Exposure to 17α-E2 reduces body weight and extends lifespan in male mice while mitigating metabolic and age-related chronic inflammation (Stout et al., 2017). The fact that 17α-E2 extends longevity of male but not female mice suggests a sexual dimorphism in its effect on lifespan (Strong et al., 2016; Harrison et al., 2014) that is reminiscent of acarbose (Harrison et al., 2014). Gonadectomised male and female mice have shown the contribution of sex hormones as main regulators of sexual dimorphism toward the lifespan extension properties of 17α-E2 and acarbose (Garratt et al., 2017). A recent study has shown that 17α-E2 treatment in male mice does not increase the contribution of protein synthesis to proteostatic processes in metabolically active tissues, contrary to what has been shown in energy-restricted models or long-lived organisms (Miller et al., 2019). Further studies are required to elucidate the molecular mechanism of 17α-E2 action.

2.2.3. Acarbose—Acarbose is an alpha-glucosidase inhibitor that inhibits intestinal digestion of carbohydrates. Used for more than 20 years to treat hyperglycemia and type 2 diabetes, acarbose is considered a CR mimetic capable of lowering postprandial blood glucose levels as well as total cholesterol, triglycerides and low-density lipoprotein cholesterol levels while enhancing insulin sensitivity in mice (Yamamoto and Otsuki, 2006; Gentilcore et al., 2011; Santilli et al., 2010). As indicated above, acarbose extends median and maximal lifespan, and improves healthspan preferentially in male mice through an increase in fibroblast growth factor-21 (FGF21) and a decrease in insulin-like growth factor 1 (IGF1) (Harrison et al., 2014). The exact mechanisms of acarbose action toward healthspan remain unclear.

2.2.4. Fibroblast growth factor-21—FGF21 is a member of the FGF superfamily involved in the endogenous regulation of glucose, lipid metabolism, and inflammation (Nies et al., 2016). This protein hormone attenuates growth hormone (GH)/IGF1 signaling and has been proposed as a therapeutic target for aging and age-related incidence of diabetes and obesity (Mendelsohn and Larrick, 2012). FGF21 delays endothelial replicative senescence by protecting cells from DNA damage and premature senescence through SIRT1 (Yan et al., 2017). FGF21, via its co-receptor β-Klotho, crosses the blood brain barrier to reduce the

levels of insulin, inhibit growth, and increase corticosterone levels, thus potentially leading to the development of new treatments for obesity and metabolic disorders (Hsuchou et al., 2007; Bookout et al., 2013). Transgenic overexpression of FGF21 extends lifespan in mice without reducing food intake or affecting either NAD^+ metabolism or the regulation of mTOR signaling by AMPK (Zhang et al., 2012). Although the precise mechanism of action is poorly understood, FGF21 could affect longevity and healthspan through alterations of key metabolic pathways reminiscent of CR mimetics, e.g., improvement in cellular longevity through activation of autophagy, stress resistance, and survival signals while attenuating cellular growth and protein synthesis (Xie and Leung, 2017).

2.3. Drugs targeting the NAD+-dependent sirtuins

2.3.1. Resveratrol—Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenol abundant in mulberries, peanuts, and the skin of red grapes. Supplementation of the normal diet with resveratrol extends lifespan and healthspan across a variety of species from yeast, C. elegans and small mammals to non-human primates (McCormack et al., 2015; Fiori et al., 2013; Jimenez-Gomez et al., 2013; Mattison et al., 2014; Bernier et al., 2016). Resveratrol elicits beneficial health effects by suppressing inflammation, oxidative damage, tumorigenesis, and immunomodulatory activities, thereby leading to improvement of mitochondrial function and protection against obesity, cancer, and cardiovascular dysfunction (Xia et al., 2008; Shin et al., 2009; Cho et al., 2017; Wang et al., 2018a, b; Novelle et al., 2015). Recent evidence suggests an attenuation of the inflammatory response in immune and endothelial cells by resveratrol (Schwager et al., 2017), which occurs likely through activation of SIRT1 and AMPK (Ohtsu et al., 2017). Moreover, resveratrol confers neuroprotection in human neural stem cells via AMPK activation and subsequent reduction in β-amyloid-induced inflammation and oxidative stress (Chiang et al., 2018). The inhibition of high-fat diet-induced NFκB signaling pathway also explains the anti-inflammatory effect of resveratrol (Pearson et al., 2008).

A cellular model of Alzheimer's disease has helped to demonstrate that resveratrol attenuates oxidative damage through mitophagy activation (Wang et al., 2018a). Resveratrol alleviates the development of alcoholic liver injury and progression to fatty liver disease by down-regulating hepatic HIF-1α expression and mitochondrial ROS production (Ma et al., 2017). Low dose of resveratrol improves mitochondrial respiratory function and enhances cellular reprogramming in patient-derived fibroblasts with mitochondrial DNA mutations (Mizuguchi et al., 2017). More recently, it has been shown that treatment of diabetic mice with resveratrol increases mitochondrial biogenesis and inhibits the activation of mitophagy in skeletal muscle, thus ameliorating diabetes-induced skeletal muscle atrophy (Wang et al., 2018b).

Although resveratrol exhibits some CR-like benefits on healthspan, its limited absorption and bioavailability are impediment to its effective use. Several studies have shown over the past years that the concentration of resveratrol and its metabolites in urine and plasma are very heterogeneous among individuals on resveratrol supplementation, suggesting that some genetic factors, especially genes from the CYP450 enzymes, could be affecting the response to resveratrol treatment (Walle et al., 2004; Ortuño et al., 2010; Chang et al., 2001). In older

community-dwelling adults, total urinary resveratrol metabolite concentration derived from normal diet was not associated with inflammatory markers, cardiovascular disease, and/or cancer or predictive of all-cause mortality (Semba et al., 2014). McDermott et al. (2017) found that resveratrol supplementation didn't improve walking performance in older people with peripheral arterial disease. Similarly, Pollack et al. (2017) showed that resveratrol treatment improved vascular function and mitochondrial number but not glucose metabolism or insulin sensitivity. Conflicting results have been shown about the effects of resveratrol in lifespan extension in mice, with some authors reporting no pro-longevity effect (Pearson et al., 2008; Miller et al., 2011; da Luz et al., 2012) while others found positive benefits of resveratrol when mice were fed high-fat diet or under intermittent fasting feeding protocols, but not on standard diet (Novelle et al., 2015; Strong et al., 2013; Pearson et al., 2008; Pallauf et al., 2016).

The molecular mechanisms of action of resveratrol remain elusive; however, AMPK and the NAD^+-dependent deacetylase SIRT1 have been proposed to mediate the anti-aging response and disease protection of resveratrol, reminiscent of CR signaling (Baur et al., 2006; Park et al., 2012; Kulkarni and Canto, 2015). Understanding how resveratrol exerts its beneficial effects in healthspan will help to develop new drugs to treat age-associated metabolic disorders.

2.3.2. Sirtuin-activating compounds (STACs): SRT1720, SRT2104 and SRT3025—

SIRT1 and the other six members (SIRT2–7) of the highly conserved class III histone deacetylase family are positively associated with lifespan (Hubbard and Sinclair, 2014). These seven mammalian sirtuins have different subcellular locations and functional properties, and their activation have been linked to delayed aging, improved metabolism, and oxidative stress resistance in different animal models (Sinclair and Guarente, 2014). Compared to resveratrol, sirtuin-activating compounds (STACs) show better potency, solubility, and target selectivity by binding to the N-terminal domain in SIRT1 (Sinclair and Guarante, 2014), which results in the activation of pro-longevity pathways that target oxidative stress, inflammation and mitochondrial function (Imai and Guarente, 2016; Nogueiras et al., 2012). Pharmacological activation of SIRT1 with SRT1720 and SRT2104 promotes healthspan and lifespan extension via reduction of inflammatory pathways (Minor et al., 2011; Mitchell et al., 2014; Mercken et al., 2014; Bonkowski and Sinclair, 2016). SRT1720 inhibits circulating TNF-α and IL-6 levels in a mouse model of estrogen-induced cholestatic liver injury (Yu et al., 2016), and postnatal administration of SRT1720 attenuates obesity and insulin resistance in offspring of mice dams fed high-fat diet during pregnancy (Nguyen et al., 2018). SRT1720 treatment lowers multi-organ injury and inflammation in mice via reduction of sepsis-induced inflammasome activation, thus attenuating renal fibrosis through apoptosis and reduction of oxidative stress (Ren et al., 2017). Furthermore, SRT1720 confers protection against endothelial senescence, resulting in the maintenance of cellular function via Akt/eNOS/VEGF axis (Li et al., 2016). Aged human mesenchymal stem cells can be rejuvenated by SRT1720-mediated SIRT1 activation of apoptosis (Liu et al., 2017). Another characterized STAC, SRT2104, has been found to increase mitochondrial oxidative phosphorylation and to decrease serum cholesterol and triglycerides in older adults (Libri et al., 2012). Treatment of diet-induced obese mice with SRT2104 promotes body

weight loss, improves insulin sensitivity, and increases exercise capacity (Qi et al., 2010); however, these benefits have not been reported in humans (Baksi et al., 2014). Short-term use of SRT2104 extends survival of male mice and preserves bone and muscle mass in an experimental model of atrophy (Mercken et al., 2014). Clinical trials involving patients with type 2 diabetes have shown SRT2104 to be associated with weight loss and improved glycemic control without effects on lipids or platelet function (Noh et al., 2017). Administration of SRT2104 in participants with diabetes lessened aortic endothelial dysfunction via inhibition of p53 (Wu et al., 2018). SRT2104 treatment confers neuroprotection and lifespan extension in a mouse model of Huntington's disease by virtue of its ability to cross the blood-brain barrier and attenuate brain atrophy while improving motor function (Jiang et al., 2014). A third characterized and selective SIRT1 activator, SRT3025, has been linked to hematopoietic stem cell expansion (Zhang et al., 2015) and inhibition of osteoclast generation and function in bone marrow-derived macrophages, a finding suggestive of a role for STACs in combatting osteoporosis (Gurt et al., 2015).

Despite extensive evidence for the delay of phenotypic aging and age-related diseases, more research is needed to elucidate the positive benefits of STACs to treat inflammation, metabolic disorders, and neurodegenerative diseases. See the recent review on the role of STACS in aging by Bonkowski and Sinclair (2016).

2.3.3. Drugs targeting NAD biosynthesis—Interventions such as CR and exercise increase the levels of nicotinamide adenine dinucleotide (NAD^+), thus resulting in improved mitochondrial function (Canto et al., 2010; Liu et al., 2008). The decline in cellular NAD^+ concentrations with aging is associated with neurodegeneration and other pathologies that adversely impact healthspan and lifespan; conversely, modulation of NAD^+ levels appears to be a key factor for successful aging (Gomes et al., 2013; Gong et al., 2013; Mouchiroud et al., 2013). NAD^+ fuels reduction-oxidation reactions and regulates a variety of biological processes, including metabolism and stress response, and mediates also some of the beneficial pro-longevity effects of intermittent fasting and CR, possibly through sirtuin activation (Bonkowski and Sinclair, 2016; Rajman et al., 2018; Imai and Guarente, 2016). The circulating levels of extracellular nicotinamide phosphoribosyltransferase (eNAMPT) significantly decline with age in mice and humans. eNAMPT is carried in extracellular vesicles (EVs) and enhances NAD^+ biosynthesis to increase lifespan in mice (Yoshida et al., 2019). Diet supplementation with nicotinamide, a NAD^+ precursor, has been recently reported to protect liver function, glucose metabolism and overall health of old mice on high-fat diet without beneficial effect on lifespan (Mitchell et al., 2018). Earlier studies with two other NAD^+ precursors, namely nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), have been found to extend healthspan and lifespan in Drosophila and yeast (Anderson et al., 2003; Balan et al., 2008). Administration of NMN ameliorates the impact of maternal obesity on offspring liver health in mice (Uddin et al., 2017) as well as cognitive function via neurovascular coupling in old mice (Tarantini et al., 2019). Improvement in endothelial blood flow and physical endurance in old mice on NMN is the result of SIRT1-dependent increase in both capillary density and hydrogen sulfide production (Das et al., 2018). Renal SIRT1 activity and NAD^+ content are restored upon NMN treatment of young

and 20-month-old mice (Guan et al., 2017), and NMN can synergize with exercise to delay skeletal muscle dysfunction in aging rats via increase in SIRT1 activity (Pajk et al., 2017).

In a mouse model of Alzheimer's disease, NR treatment reduces DNA damage, neuroinflammation, and apoptosis of hippocampal neurons while promoting an increase in brain SIRT3 activity that leads to an improvement in cognitive function and hippocampal synaptic plasticity (Hou et al., 2018). NR supplementation attenuates the development of heart failure in a mouse model of dilated cardiomyopathy (Diguet et al., 2017), and stimulates hematopoiesis through increased mitochondrial clearance in immunodeficient mice (Vannini et al., 2019).

In humans, a recent clinical trial showed that chronic NR supplementation is well tolerated and stimulates NAD^+ metabolism in healthy middle-aged and older adults (Martens et al., 2018).

As a whole, these results indicate that supplementation with NAD^+ precursors is a promising intervention strategy to delay aging and reduce age-associated ailments. However, pharmaco-kinetics or pharmacodynamics studies with these compounds are missing and more work is needed to elucidate the exact mechanisms by which these drugs can improve healthspan and lifespan.

2.4. Interventions targeting amino acid pathways

Although the reduction in calorie intake does not always extend lifespan (Mattison et al., 2012; Mitchell et al., 2016), restriction in specific dietary components, such as proteins or amino acids, has been linked to the control of lifespan from yeast to humans (Leto et al., 1976; Grandison et al., 2009; McIsaac et al., 2016). The mechanisms underlying the role of methionine and other amino acids in delaying aging remain unclear, but may involve reductions in serum IGF-1 coupled with lower oxidative stress and autophagy (Mirzaei et al., 2014; Ables and Johnson, 2017; Liu et al., 2015). Animals on methionine- or tryptophan-restricted diets live longer and show significant reduction in age-related diseases partly though detoxification of mitochondrial ROS (Gonzalez-Burgos et al., 1998; Edwards et al., 2015; Obata and Miura, 2015; Gomez et al., 2015). Adipose tissue and liver are particularly responsive to methionine restriction (Ghosh et al., 2014; Wanders et al., 2015, 2016; Ables and Johnson, 2017), although other organs such as brain, heart and kidneys also benefit from this intervention (Cooke et al., 2018; Grant et al., 2016; Vogel et al., 2017; Marti-Carvajal et al., 2017). One recent study shows clear modulation of gut hormones, weight loss, energy balance, and gut microbiota in rats subjected to tryptophan restriction (Zapata et al., 2018). Moreover, the circadian clock (Nascimento et al., 2013) as well as brain plasticity and normal development (Serfaty et al., 2008) are influenced by tryptophan supplementation in mice. It is imperative that nutritional intervention studies with amino acid restriction be performed in humans.

2.5. Drugs targeting autophagy

Autophagy is a recycling mechanism that helps maintain cellular homeostasis and energetic balance (Sridhar et al., 2012; Singh and Cuervo, 2011). Several types of autophagy have been described and include macroautophagy, microautophagy, and chaperone-mediated

autophagy (Singh and Cuervo, 2011), whose effects on health and disease have garnered attention over the years. With aging, there is progressive loss of proteostasis characterized by dysregulation in autophagy, ubiquitin-mediated degradation, and protein synthesis (Lopez-Otin et al., 2013). Aging and age-related diseases have been associated with changes in polyamine levels (Minois, 2014; Gupta et al., 2013) and their role in autophagy (Basisty et al., 2018). The impact of polyamines on cell growth, survival and proliferation has been ascribed to the inhibition of DNA methylation and tumorigenesis in mice (Soda et al., 2013).

Spermidine is a naturally occurring polyamine that elicits beneficial anti-aging effects through regulation of autophagy and other mechanisms, including antioxidant protection (Madeo et al., 2018a). Moreover, spermidine mediates lifespan extension in yeast via inhibition of histone acetylases and activation of autophagy genes, such as atg7, atg11 or atg15 (Morselli et al., 2009). Spermidine extends lifespan in several animal species via MAPK pathway (Minois, 2014) and is effective in improving neurodegeneration and conferring cardioprotection through autophagy (LaRocca et al., 2013; Buttner et al., 2014; Sigrist et al., 2014; Eisenberg et al., 2016). Spermidine supplementation is safe in humans and has positive effects on cognitive function of older adults (Schwarz et al., 2018) and on blood pressure (Eisenberg et al., 2016). The recent review by Madeo et al. (2018b) provides in-depth information about the role of spermidine in aging and disease.

2.6. Drugs targeting senescence pathways

Age-related accumulation of senescent cells in various tissues and organs is associated with several deficiencies that include (1) the decline in the number of stem cells that rely on proliferation for their proper function, (2) weakening of the immune system, (3) inadequate repair capacity, and (4) reduced global and site-specific DNA methylation in aging tissues (Sidler et al., 2014; LeBrasseur et al., 2015). The clearance of p16Ink4a-positive senescent cells delays age-related disorders (Baker et al., 2011) and evidence suggests that genes implicated in cellular senescence are also linked to longevity and age-related diseases (Tacutu et al., 2011). Senolytics refer to small molecules that can induce apoptosis in senescent cells and capable of promoting lifespan extension while delaying the onset of age-related diseases (Kirkland et al., 2017). Originally developed as common anticancer drugs, navitoclax, quercetin, and dasatinib have senolytic properties (Ranganathan et al., 2015; Tolcher et al., 2015) that target BCL-2 and related anti-apoptotic pathways (Zhu et al., 2017). Alvespimycin is a potent HSP90 inhibitor with senolytic properties (Fuhrmann-Stroissnigg et al., 2017). Other senolytics include fisetin, a naturally-occurring flavone with low toxicity, and the BCL-XL inhibitors, A1331852 and A1155463, that have similar reactivity as navitoclax but with less hematological toxicity (Zhu et al., 2017). Clearance of senescent cells with chronic senolytic treatment improves age-related vascular conditions and reduces mortality from cardiovascular disease (Roos et al., 2016). For example, the treatment of aged mice with navitoclax eliminates senescent cardiomyocytes and attenuates profibrotic protein expression in aged mice (Walaszczyk et al., 2019). The combination of dasatinib plus quercitin has been recently shown to improve physical function and increase lifespan in old mice (Xu et al., 2018) and ameliorates Aβ plaque-associated inflammation and cognitive deficits in Alzheimer's disease mice (Zhang et al., 2019).

The ability of senolytic drugs to reduce the number of senescent cells and combat inflammatory diseases, such as obesity and other metabolic disorders, constitutes a major therapeutic approach aimed at ensuring healthy aging (Palmer et al., 2019). In fact, an open-label pilot clinical study has recently demonstrated that quercitin could alleviate idiopathic pulmonary fibrosis (Justice et al., 2019). The recent review of Kirkland et al. (2017) provides additional insight into this important class of compounds.

2.7. Rejuvenation factors (GDF11, GDF8)

Studies of heterochronic parabiosis have provided evidence of rejuvenation factors present in the blood of young mice (e.g., cells and proteins) that provide benefits in aged animals (Conboy et al., 2005). Systemic administration of young blood counteracts age-related decline in cognitive function and synaptic plasticity in mice (Villeda et al., 2014). Growth/differentiation factor 11 (GDF11) and GDF8, both members of the transforming growth factor (TGF)-β superfamily, have been identified as rejuvenation factors (Loffredo et al., 2013; Sinha et al., 2014). Circulating concentrations of GDF11 correlate with lifespan in mice (Zhou et al., 2016), and several studies have shown that the decline in circulating GDF11 in old mice can be restored, via parabaiosis or injection of the recombinant form, with concomitant reduction in age-related cardiac hypertrophy (Loffredo et al., 2013; Sinha et al., 2014). Daily injections of GDF11 also improves cerebral vasculature and increases the number of brain stem cells (Katsimpardi et al., 2014). However, other studies have reported the lack of pro-longevity effects of GDF11 in a mouse model of premature aging (Freitas-Rodriguez et al., 2016), and GDF11 treatment does not appear to rejuvenate skeletal muscle stem cells in old mice (Hinken et al., 2016). In humans, there is no evidence to suggest that GDF11 levels decline with age, although low GDF11 has been associated with frailty and morbidity in older adults with cardiovascular disease (Schafer et al., 2016).

The contribution of these rejuvenation factors in aging research has been controversial (Egerman et al., 2015; Smith et al., 2015), and it is based mostly on the lack of accuracy in quantifying GDF11 and GDF8. More work is needed to assess whether these and other rejuvenation factors can reverse aging phenotypes in both mice and its potential translation into humans.

3. Where are we now?

3.1. Compounds tested for anti-aging activity in mice via the National Institute on Aging (NIA) Interventions testing Program (ITP)

The Interventions Testing Program (ITP), developed in 2003 by the NIA at the National Institutes of Health (NIH), was designed to capitalize on the information previously reported on identified genes and gene products that impact healthy lifespan in non-mammalian species, and to rigorously evaluate in mice any agent that when taken in food or water could potentially delay aging rates or prevent late-life diseases (Warner, 2015). To achieve this goal, interventions are selected from the annual solicitation for collaborators by a two-level approval process and tested at three different sites simultaneously (University of Michigan, The Jackson Laboratory, and University of Texas Health Science Center in San Antonio (UTHSCSA) (Miller et al., 2007)). Key central features of this program include 1) the use of

genetically heterogeneous mice (UM-HET3) obtained by a specific four-way crossbreeding scheme (CB6F1 females bred to C3D2F1 males), 2) the use of sufficient statistical power to detect 10 % changes in lifespan, in either sex, 3) the use of pair-fed and untreated controls, 4) the minimal inclusion of age-sensitive traits (i.e: locomotor activity, T-lymphocyte subtypes, and hormornes such as insulin, IGF-1, leptin and thyroxine), 5) plans for necropsy analysis, and 6) plan for interim analyses of survival (Miller et al., 2007). Grounded on these unique characteristics, the ITP has tested so far 67 interventions with 42 different compounds (Table 1). The efficiency/effects of the compounds are presented in Fig. 2 and have been published in several articles (https://www.nia.nih.gov/research/dab/interventions-testing-program-itp/publications-nia-interventions-testing-program).

Perhaps the best known finding by the ITP is that rapamycin increases lifespan of both male and female mice (Harrison et al., 2009; Miller et al., 2011). The beneficial effects of rapamycin are seen when administration began at 270 days and later at 600 days of age, which suggests that it could have therapeutic potential in humans even if started late in life. Most recently, the ITP has conducted a dose-response study and found that concentrations of rapamycin higher than those used in the original studies can actually increase the maximal lifespan of mice (Miller et al., 2014). Rapamycin delays the progression of multiple age-related pathologies including liver degeneration, endometrial hyperplasia in females, and the appearance of abnormal cell nuclei in the heart (Wilkinson et al., 2012). However, negative effects of rapamycin, such as testicular degeneration, increased severity of cataracts, and insulin-resistant phenotype, were reported indicating that caution must be used when assessing the potential role of rapamycin in lifespan extension (Wilkinson et al., 2012; Miller et al., 2014). Surprisingly, in the context of type 2 diabetes, rapamycin has cardioprotective effects and positive benefits on glucose metabolism (Azar et al., 2018; Reifsnyder et al., 2016).

Acarbose has also been found to increase median and maximal lifespan in both sexes when administered early in life, although the effects of acarbose were much larger in males (Harrison et al., 2014, 2019). Starting the acarbose treatment at 16 months of age resulted in an extension of maximum lifespan for both sexes, with an increase in median longevity observed only in males (Strong et al., 2016).

Other ITP studies have shown that only males have increased median lifespan when given either aspirin, nordihydroguaiaretic acid (NDGA), 17-α-estradiol, or protandim (Harrison et al., 2014; Strong et al., 2016, 2008). Originally, it was thought that differences in the metabolism of aspirin and NDGA could be responsible for their sex-specific effects on lifespan; however, administration of high dose NDGA failed to improve the lifespan of females despite achieving plasma NDGA concentrations similar to the males in the original study (Harrison et al., 2014). Therefore, the refractoriness of female mice to NDGA cannot simply be accounted for by differences in pharmacodynamics. Gonadal hormones underlie male-specific metabolomics response to 17-α-estradiol and improvements in glucose tolerance and mTORC2 signaling (Garratt et al., 2017).

The control male mice at UTHSCSA and The Jackson Laboratory have shorter lifespan than at the University of Michigan, while the females have relatively similar lifespans at all three

sites (Harrison et al., 2014). This fact may partially explain why in general the tested interventions preferentially benefit males compared to females. Nevertheless, other complex variables can be at play.

Most of the interventions tested by the ITP, as well as those reported here, did not produce significant effects on lifespan in mice regardless of sex (Fig. 3). These include 4–OH-α-phenyl-*N*-tert-butyl nitrone (4–OH-PBN), nitroflurbiprofen (NFP), caffeic acid phenethyl ester (CAPE), enalapril maleate, simvastatin, resveratrol, green tea extract, curcumin, oxaloacetic acid, medium-chain triglyceride oil, metformin, fish oil, and ursodeoxycholic acid (UDCA) (Harrison et al., 2009; Miller et al., 2011; Strong et al., 2016, 2008; Strong et al., 2013). Methylene blue increases maximal, but not median, lifespan only in female mice (Harrison et al., 2014). Some of these findings are inconsistent with reports from other laboratories (Baur et al., 2006; Kitani et al., 2007; Martin-Montalvo et al., 2013; Anisimov et al., 2015; Bartke et al., 2019) and variables such as the age of onset, genetic background, dosage, mode of delivery, diet composition, and treatment regimen could account for these discrepancies. It is also possible that some of these interventions had other long-term effects, positive or negative, on other measurements of health, which were not detected due to the sole focus of the ITP on lifespan.

3.2. Other compounds that are being tested in the NIA-ITP

The ITP is testing another 22 compounds, although no data has been reported yet (Table 2).

3.3. Translation of the NIA-ITP findings toward the clinic in the treatment of age-associated chronic diseases

The goal of treating chronic conditions and common geriatric syndromes is to enhance the quality of life and reduce mortality in the elderly. Using ClinicalTrials.gov, a database of privately and publicly funded clinical studies conducted around the world, we surveyed the most recent number of clinical trials (until July 2019) that treat aging or age-related diseases with the compounds/drugs described in Section 2 of the manuscript. All these clinical trials are being tested in both male and female participants of various ages (Supplementary Table 1). The bulk of these studies are interventional or observational, and tackle a number of age-related medical conditions ranging from insulin resistance and diabetes to dementia and cancer. Drug combinations are also being tested, including rapamycin with acarbose or with metformin as well as interventions such as CR with exercise.

In the database "condition/disease" is defined as "*The disease, disorder, syndrome, illness, or injury that is being studied".* On ClinicalTrials.gov, conditions may also include other health-related issues, such as *"lifespan, quality of life, and health risks*", and "Intervention/Treatment" as "*A process or action that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include noninvasive approaches, such as education or modifying diet and exercise". Our search for* conditions or disease included the terms: "age", "aging," "longevity", "lifespan", "senescence", "frailty," "sarcopenia", "age-related atrophy", "type 2 diabetes", "metabolic syndrome," "cardiovascular disease", "age-related macular degeneration", "age-related cognitive

decline", "dementia", "mild cognitive impairment", "Alzheimer Disease", "Parkinson Disease", "cancer", "osteoporosis" and "osteoarthritis". For interventions and treatments: "acarbose", "aspirin", "curcumin", "estradiol", "GDF8″", "myostatin", "GDF11″", "green tea", "metformin", "methylene blue", "NAD", "nicotinamide", "nicotinamide riboside, "NAD precursors", "polyamines", "quercitine", "resveratrol", "sirtuin-activating compounds", "SRT2104″", "SRT3025″", "simvastatin", "tryptophan", "ketogenic diet", "caloric restriction", "dietary restriction", "exercise" and "fasting". We found ~12,100 clinical trials that target age or age-related diseases with more than 538 clinical trials aimed toward "Aging as a condition or disease" Table 3). Table 3 describes all the clinical trials available by drug and age or age-related conditions. Many of these trials differ dramatically by sample size and, thus, interpreting the study results will require caution. Note the absence of GDF11 and 17 α-estradiol due to a lack of experimental intervention in clinical trials. Exercise, fasting and CR are the interventions with the highest number of clinical trials that target aging as a condition (435, 20 and 15 trials, respectively), followed by NAD precursors (12), metformin (11), and resveratrol (10).

4. Limitations and caveats

Older adults suffer from multiple medical conditions or co-morbidities and more than half take five or more medications, which raises the issue of polypharmacy leading to compliance concerns, adverse effects, and potential risk of drug-drug interactions. Moreover, environment, nutrition, age, ethnicity, and gender are important variables that contribute to differential responses to treatment or interventions. Indeed, there are substantial evidences pointing toward drug toxicity only at a certain age interval. Four possible outcomes have been ascribed within a cohort of patients having the same diagnosis and receiving the same prescription: 1) Drug toxic but beneficial; 2) drug toxic but not beneficial; 3) drug not toxic and not beneficial; and 4) drug not toxic and beneficial (Harrill, 2016). It would appear, therefore, that only few patients at a certain age range are expected to respond adequately to standard therapy, with most patients being either non-responders, develop resistance, or exhibit an inadequate response (Harrill, 2016). An example at hand is the hepatotoxicity to commonly used drugs, such as acetaminophen and ibuprofen, in sensitive individuals (Chitturi and George, 2002).

People age at different rates and the age-related deterioration and functional decline vary within the same individual in a tissue-specific manner: Epigenetic changes, such as DNA methylation and histone modification, largely account for the dynamic alteration in the transcriptional profile and/or cellular phenotype in a given tissue with age (Horvath, 2013; Melis et al., 2013). It has been assumed, wrongly perhaps, that the promotion of healthy aging, notably through delay in the aging phenotypes, frailty and associated geriatric syndromes, will impact every biological system to the same extent (Michel et al., 2016). However, whether changes in the number, dose frequency, and treatment length of medications influence physiological outcomes and cellular epigenetic landscapes within different types of tissues and organs remain to be answered. There is still a lack of clinical evidence for healthspan extension through compression of chronic disease in late life and it remains possible that some of the age–related phenotypic declines in function might not respond adequately to treatment (responders vs. non responders) (Evert et al., 2003;

Atkinson et al., 2019). Therefore, successful assessment in the efficacy of an intervention that delays aging will require validation through stringent outcome measures of phenotypic enhancement of longevity in various biological systems. The emergence of age-related changes within each type of tissue, whether at the genome, transcriptome, proteome, or metabolome level, should enable the identification of a selective set of biomarkers of aging and validate the efficacy of an intervention aimed at preserving or maintaining tissue functionality. Yet, with the advances in the different fields of molecular biology, the search for biomarkers or predictors of biological and phenotypic age, rather than chronological age, remains unsuccessful, except the epigenetic clock developed by Horvath in 2013. Ideally, defining those predictors for 'healthy aging' will allow us to predict lifespan.

Very few animal models, with the exception of non-human primates, adequately replicate physical and biochemical deficits in terms of human aging and age-related diseases. The rhesus monkey (Macaca mulatta) genome shares 93 % sequence identity with the human genome, and most of their anatomy, physiology, neurology, endocrinology, immunology an ddecline in function with age directly parallel those of humans, making this species an excellent model to study human aging. It is imperative to develop new animal models that better mimic key clinical features of human aging phenotypes and their environments for use in preclinical studies. Recently, researchers at university of Washington in Seatle, initiated an intervention study The Dog Aging Project, 2020 (http://dogagingproject.com) aiming to perform a longitudinal study of aging in dogs and an intervention trial to test whether rapamycin will prevent disease and extend healthy longevity in middle-aged dogs.

Pharmacological interventions need to satisfy the following conditions in order to be translatable: i) Low toxicity and few side effects; ii) effective via oral administration, iii) maximum dosing frequency of once-a-day; iv) stability; v) scalability and low manufacturing costs; vi) detectable in blood; and vii) effective when administered late in life or once symptoms have already started to develop (Kirkland, 2016). It remains to be seen whether long-term exposure of middle-aged adults to an 'anti-aging drug' will confer longevity dividend (described by Olshansky et al., 2016 as "*the economic and health benefits that would accrue to individuals and societies if we extend healthy life by slowing the biological processes of aging*").

Perhaps, one of the main obstacles for the development of drugs to treat aging is that the FDA does not consider aging as a preventable condition. However, the FDA has recently agreed of a new clinical trial aimed at testing the ability of the diabetes drug metformin at delaying or preventing diseases associated with old age, including heart disease, cognitive impairment, and cancer (Barzilai et al., 2016). Metformin could be the first drug of its kind to be repurposed with the goal of targeting aging. If successful, similar studies will surely follow with other compounds, with the goal of maximizing the years that we live free of diseases or chronic conditions. This compression of morbidity should shorten the time spent with age-related syndromes as humans approach the limit of their lifespan (Fries et al., 2011).

5. Conclusions and future directions

Aging is an intrinsic heterogenic feature of most living organisms, especially mammals, and recent research has provided clues about how to improve several converging cellular processes implicated in nutrient sensing, mitochondrial bioenergetics, and healthy senescence. Animal studies and human clinical trials have thought us that diet, environment, gender, ethnicity, polymorphisms, and age are among the variables that contribute to being responders or non-responders to any given therapy, whether it is cancer, cardiovascular disease, or other ailments. The extensive genetic diversity both within and among human populations generally leads to discordance in the safety and efficacy profile of a drug. It has become increasingly apparent that these different responses to treatment require the use of molecular profiling to determine the appropriate therapy. The tailoring of pharmacotherapy to the individual characteristics of each patient can be applied to areas as varied as cancer, coronary heart disease, diabetes, and neuropathological disorders to name of few (Vargas and Harris, 2016; Orho-Melander, 2015; Scheen, 2016; Golan et al., 2016). It is likely that the identification of relevant biomarkers of healthspan will enable to stratify subgroups of individuals that will respond favorably to interventions aimed at reducing age-related ailments and chronic disease (Fig. 4).

Hopefully, integration of intermediate phenotypes of different (genetic and non-genetic) origin along with ‘omics’ data sets from the genome, transcriptome, proteome, and metabolome (Williams et al., 2016), and machine learning approaches will soon enable identification of subgroups of elderly subjects with similar complex trait frequency and predict whether an individual might benefit from a treatment aimed at tackling age-associated cognitive deficits and physical frailty and geriatric syndromes. This approach should identify subgroups of the aging population that exhibit differential responses to treatment through selection of potential targetable biomarkers. It follows that the conditional probability that an elderly individual responds favorably to a given intervention will be measurably improved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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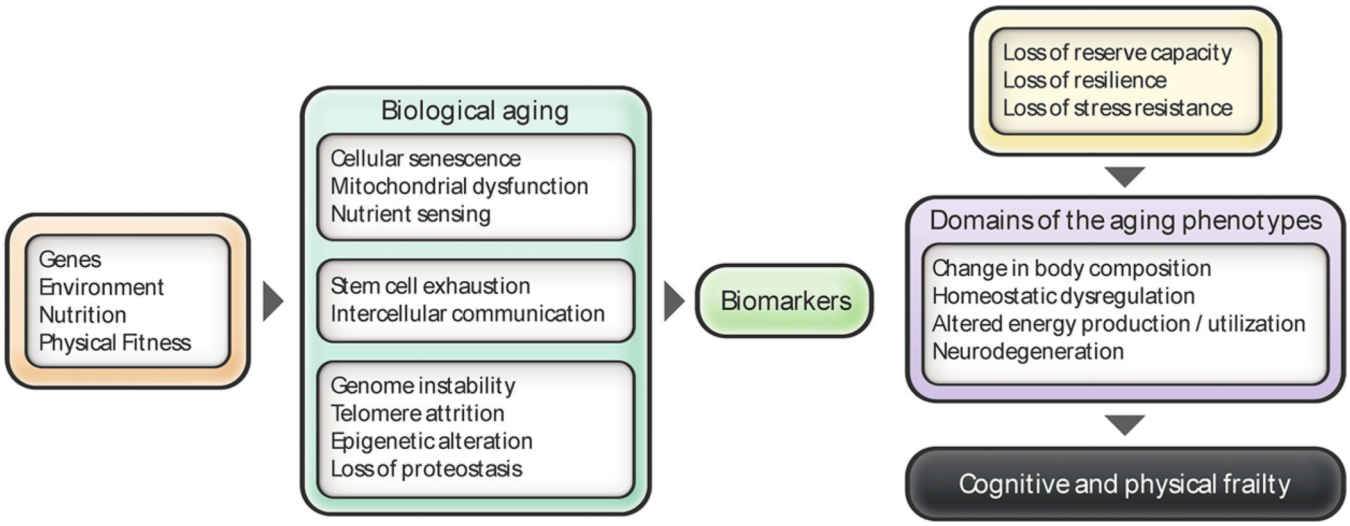

Fig. 1. Hallmarks of aging and the four domains of aging phenotypes.

Integrative view of the hallmarks of aging described by Lopez-Otin et al. (2013) and the domains of the aging phenotypes described by Ferrucci et al. (2010). Different factors (genes, environment, exercise and nutrition) contribute to the rate of biological aging. The loss of reserve capacity or resilience, at a molecular and cellular level, ultimately leads to the development of the aging phenotypes.

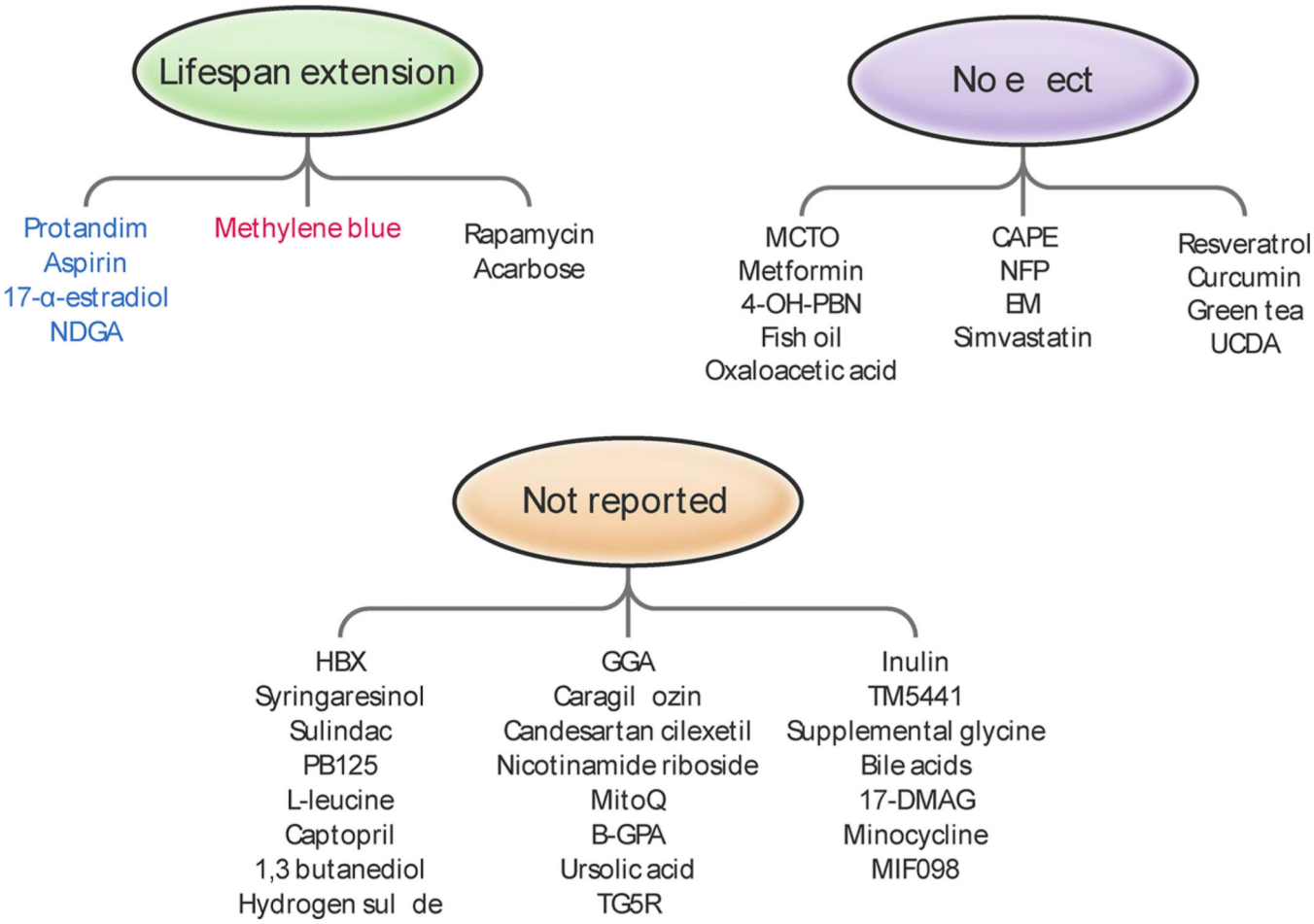

Fig. 2. Compounds tested by the National Institute on Aging (NIA) Interventions Testing Program (ITP) for their anti-aging activity and effects on lifespan extension in mice.

Some compounds elicit anti-aging effects on lifespan that are sex-dependent. For instance, rapamycin and acarbose extend lifespan in both sexes whereas methylene blue (in red) has pro-longevity effects only in females. Four compounds (in blue) extend lifespan in males. Most of the compounds are still being tested and there is no data available.

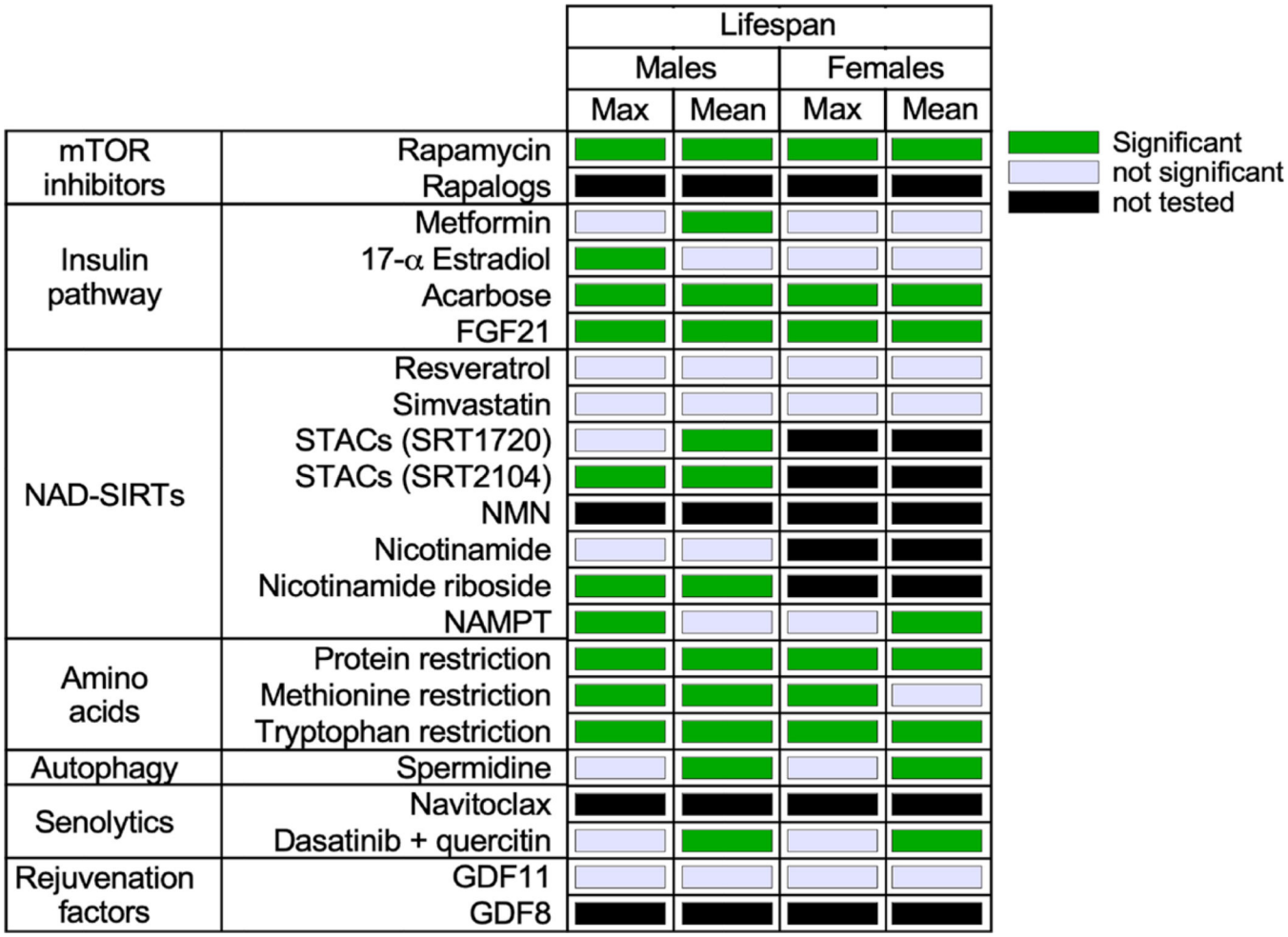

Fig. 3. Heatmap summarizing the different interventions and their effect in maximum and mean lifespan extension in mice.

These interventions target major signaling pathways whose dysregulation contributes to the emergence of the aging phenotypes and disease.

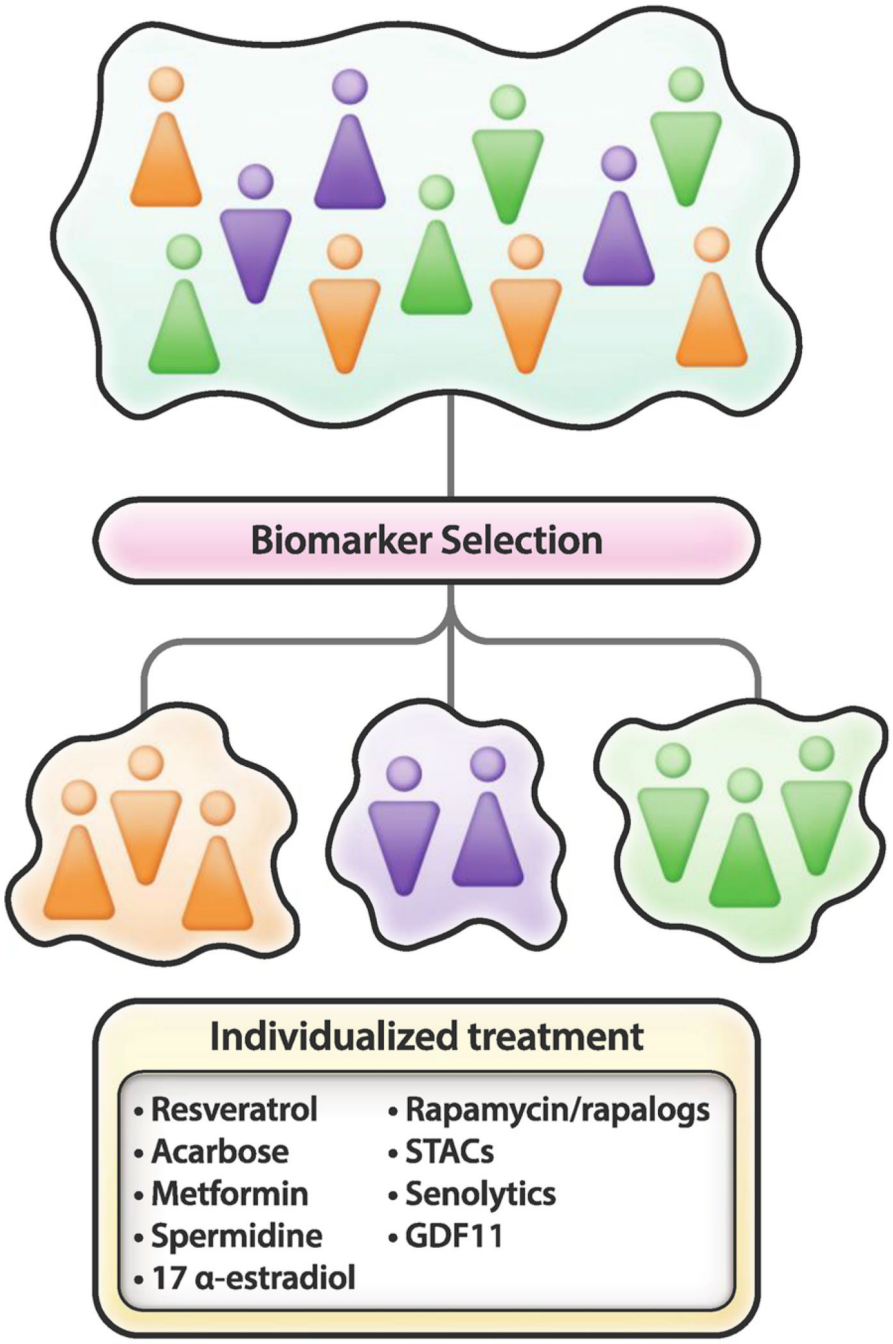

Fig. 4. Personalized approach for the treatment of age and age-related diseases.

The identification of relevant biomarkers of healthspan and the integration of 'omics' data sets from the genome, transcriptome, proteome, and metabolome, and machine learning approaches, will likely allow the development of personalized treatments aimed at reducing age-related diseases.

Table 1

Compounds under testing in the NIA-ITP. The ITP has tested so far 67 interventions with 42 different compounds.

COMPOUND	CONCENTRATION IN FOOD (PPM)	AGE AT TREATMENT INTIATION (MONTHS)	Effect on lifespan
Aspirin	20	4	
	60	11	Males
	200	11	
NFP	200	4	None
NDGA	2500	9	
	800	6-male	
	2500	6-male	Males
	5000	6	
	2500	13	
	5000	13	
4-OH-PBN	315	4	None
CAPE	30	4	
	300	4	None
Enalapril Maleate	120	4	None
Rapamycin	14	20	
	14	9	
	4.7	9	Males
			Females
	14	9	
	42	9	
	42	20	
Simvastatin	12	10	
	120	10	None
Resveratrol	300	12	
	1200	12	None
	300	4	
Oxaloacetic acid	2200	4	None
Green tea extract	2000	4	None
Curcumin	2000	4	None
Medium Chain Triglyceride Oil	60000	4	None
17a-Estradiol	4.8	10	
	14.4	10	Males
	14.4	16 and 20	
Methylene Blue	28	4	Females
Acarbose	1000	4	
	1000	16	
	2500	8	Males
			Females

COMPOUND	CONCENTRATION IN FOOD (PPM)	AGE AT TREATMENT INTIATION (MONTHS)	Effect on lifespan
	1000	8	
	400	8	
Fish Oil	15000	9	None
	50000	9	
Bile acids	5000	5	-
Metformin	1000	9	
Protandim **	600	10	Male
INT-767 FXR/TG5R agonist	180	10	-
HBX	1	15	Males
Ursolic acid	2000	10	-
Glycine	80000	9	-
TM5441-inhibitor of PAI-1	60	11	Males
Inulin	600	11	Males
17-DMAG	30	6	-
MitoQ	100	7	Males
Minocycline	300	6	-
B-GPA	3300	6	-
MIF098	240	8	Males
Nicotinamide Riboside	1000	8	None
Canagliflozin	180	7	-
Candesartan cilexetil	30	8	-
Geranylgeranylacetone	600	9	-
Hydrogen Sulfide - SG1002	240	TBD	-
1,3-butanediol	100000	6	Males
Captopril	180	5	-
L-leucine	40000	5	Males
			Females
PB125	100	5	-
Sulindac	5	5	-
Syringaresinol	300	5	-
Metformin + Rapamycin	1000 / 14	9	Males
			Females
Rapamycin + Acarbose	14.7 / 1000	9 and 16	-

- no data available.

* ppm (part per million by weight).

** the Protandim® was increased from 600 ppm to 1200 ppm when the mice reached 17 months of age.

Table 2

Compounds under testing in the NIA-ITP with no data reported to date.

Compound	Classification/ Properties	Primary and secondary effects	Reference
1,3-Butanediol	Precursor of the ketone body β-hydroxybutyrate (β-HB)	• Ketogenic diets increase levels of β-HB and have been shown to improve healthspan, memory, and longevity in mice	Newman et al., 2017; Roberts et al., 2017
17-DMAG	Derivative of the benzoquinone ansamycin antibiotic geldanamycin	• Inhibitor of the ATPase function of HSP90 with anti-inflammatory properties in autoimmune and neurodegenerative diseases, as well as obesity and metabolic diseases. • Prolongevity effects via reduction of acetyl-CoA levels with concomitant stimulation of autophagy.	Calamini and Morimoto, 2012; Tukaj and Węgrzyn (2016); Verma et al., 2016; Ambade et al., 2014; Madeo et al., 2014
2-(2-hydroxyphenyl)-benzoxazole (HBX)	Metal chelator and anti-aggregation properties	• Increases lifespan in C. elegans. • Increases lifespan in ALS mouse model.	Alavez et al., 2011; Evans et al., 2016
β-guanidinopropionic acid (β-GPA)	Analogue of creatine that competitively inhibits creatine kinase and depletes intracellular phosphocreatine and ATP levels	• Activates AMPK and promotes mitochondrial biogenesis in skeletal muscle in rats. • Extends lifespan in flies via AMPK.	Oudman et al., 2013; Reznick et al., 2007; Yang et al., 2015
Bile acids	Steroid acids	• Dietary absorption of lipids and the fat-soluble vitamins A, D, E and K. • Activation of nuclear hormone receptors, mainly the farnesoid X receptor (FXR), controlling hepatic lipid and glucose metabolism. • Activation of G protein-coupled receptor TGR5, acting on the immune system response, energy expenditure, glucose homeostasis, and insulin sensitivity. • Extends yeast chronological lifespan in a TOR-independent manner (lithocholic acid). • Modulates lifespan in *C. elegans* through nuclear receptor signaling (dafrachronic acid).	Russell, 2009; Trauner et al., 2010; Pols et al., 2011; Rizzo et al., 2010; Watanabe et al., 2012; Goldberg et al., 2010; Beach et al., 2013, 2015; Gerisch et al., 2007; Magner et al., 2013; Amador-Noguez et al., 2007
Canagliflozin	Sodium-glucose co-transporter-2 (SGLT2) inhibitor convoluted tubule of the kidney, thereby facilitating the excretion of glucose in the urine. • Caloric restriction mimetic.	• Blocks the reabsorption of glucose in the proximal	Kalra, 2014; Kalra et al., 2016
Candesartan cilexetil	Prodrug form of candesartan, an angiotensin II receptor antagonist	• Increases the lifespan of spontaneously hypertensive rats.	Baiardi et al., 2004
Captopril	Angiotensin-converting enzyme (ACE) inhibitor	• Extends lifespan in nematodes via a mechanism that is distinct from calorie restriction.	Kumar et al., 2016
Geranylgeranylacetone (GGA)	Inducer of the 70-kDa heat shock protein (HSP70)	• Prevents hearing loss and hair cell death in a mouse model of age-related hearing loss. Positive effects on cognition and Aβ pathology in the APP23 mouse model of Alzheimer's disease.	Hirakawa et al., 1996; Hoshino et al., 2013
Glycine	Methionine restriction mimetic	• Increases lifespan in flies and in rats.	Sugiyama et al., 1987; Orentreich et al., 1993; ;Obata and Miura, 2015
Inulin	Bifidogenic and fiber-like compound	• Regulates GLP-1 and ghrelin levels for the control of food intake and appetite, stimulates the immune system, improves mineral absorption and bone mineralization, influences blood and liver lipid metabolism. • Reduces the risk of chronic gastrointestinal track and colon cancer. • Increases lifespan in rats. • Increase muscle strength in humans. • Anti-inflammatory effects via gut microbiota.	Milani et al., 2016; Tuohy, 2007; Shoaib et al., 2016; Rozan et al., 2008; Buigues et al., 2016
L-Leucine	Branched chain amino acid (BCAAs)	• Extends lifespan in yeast, nematodes, and mice. • Stimulates protein synthesis in skeletal muscle via mTOR pathway. • Increases functional performance and lean tissue mass in elderly humans.	Alvers et al., 2009; D'Antona et al., 2010; Mansfeld et al., 2015; Norton and Layman, 2006; Ispoglou et al., 2016

Compound	Classification/ Properties	Primary and secondary effects	Reference
Minocycline	Semi-synthetic, second-generation tetracycline analogue	•Antioxidant properties, anti-inflammatory/immunomodulatory effects, and neuroprotection mainly by inhibition of microglia activation and attenuation of apoptosis. • Inhibits the formation of kynurenine from tryptophan, mechanism implicated in age-related metabolic disorders as well as psychiatric disorders • Improves healthspan and lifespan in Drosophila.	Garrido-Mesa et al., 2013; Oxenkrug et al., 2012; Oxenkrug, 2013; Mora et al., 2013
MitoQ	Antioxidant ubiquinone conjugated to a lipophilic cation with anti-apoptotic effects	• Delays the onset of paralysis and increase lifespan in C. elegans model of AD.; • Increases lifespan in flies. • Increases lifespan in ALS mouse model.	Kelso et al., 2001; Ng et al., 2014; Magwere et al., 2006; Miquel et al., 2014
MIF098	Interferes with the ability of macrophage migration inhibitory factor (MIF) cytokine to bind to its receptor, CD74	• Inhibition of MIF extends lifespan in mice. • Anti-inflammatory effects.	Harper et al., 2010; Weiser et al., 2015; Hare et al., 2010
Nicotinamide riboside	NAD^+ precursor	• Extends lifespan by increasing NAD + synthesis in yeast.	Belenky et al., 2007
PB125	Phytochemical compound consisting of carnosol, carnosic acid, shogaol, gingerol, luteolin, and withaferin A	• Activates NRF2 pathway in mice and cells.	Hybertson and McCord, 2017 (patent)
SG1002 (sodium polysulthionate)	Prodrug of the endogenous signaling gasotransmitter hydrogen sulfide (H2S)	• Increases lifespan in a Sir2-dependent manner in C. elegans. • Prevent oxidative stress and activates sirtuins affecting nutrient-sensing pathways.	Polhemus et al., 2015; Miller and Roth, 2007; Ng et al., 2018
Sulindac	Nonsteroidal anti-inflammatory drug (NSAID) that inhibits both cyclooxygenase I and II	• Inhibit tumorigenesis, and might prevent sporadic colorectal adenomas in patients with a history of resected adenomas. • Attenuates age-related deficits in learning and memory in aged Fischer 344 rats. • Might extend lifespan in yeast, nematodes and flies (similar to ibuprofen).	Meyskens et al., 2008; Gurpinar et al., 2014; Mesches et al., 2004; He et al., 2014
Syringaresinol	Phytochemical compound found in Panax ginseng berries	• Activate Sirt1 gene expression in human umbilical vein endothelial cells and delay senescence in a FOXO3-dependent manner. • Modulates gut integrity, microbiota diversity, and delays age-associated immunosenescence. • Induces vasorelaxation in endothelial cells by increasing nitric oxide production.	Cho et al., 2013, 2016; Chung et al., 2012
TM5441	Senolytic drug via plasminogen activator inhibitor-1 (PAI-1)	• Increases lifespan in the Klotho-deficient mice. • Protection against high-fat diet-induced obesity and insulin resistance.	Boe et al., 2013; Jeong et al., 2016; Piao et al., 2016; Eren et al., 2014;
Ursolic acid	Pentacyclic triterpenoid	• Increases lifespan in C. elegans. • Increases skeletal muscle mass in human and mouse • Reduces adiposity (mouse). • Stimulates IGF-1/ AKT signaling.	Vayndorf et al., 2013; Kunkel et al., 2011, 2012

Table 3

Number of clinical trials available by drug and age or age-related condition. On ClinicalTrials.gov, "condition/disease" is defined as "the disease, disorder, syndrome, illness, or injury that is being studied". We found ~12,100 clinical trials that target age or age-related diseases with 510 clinical trials aimed toward "Aging as a condition or disease". Of note, we have added anti-aging interventions such as CR, exercise, fasting, and ketogenic diet, although they are not the focus of the review. To date, exercise is the "anti-aging" intervention with the most on-going clinical trials.

DRUGS	AGING*	AD**	AMD	CANCER	CDV	FRAILTY	MET.S**	OSTEOA	OSTEOP	PD	SARCOPENIA	T2D***
ACARBOSE	2	0	0	4	19	0	1	0	0	0	0	67
ASPIRIN	1	0	3	161	1008	0	3	2	0	0	0	53
CURCUMIN	9	5	0	65	8	0	7	4	0	0	0	8
GDF8	2	0	0	0	0	0	0	0	0	0	2	0
GREEN TEA	5	0	0	97	31	0	2	1	1	1	0	17
METFORMIN	11	3	1	335	105	4	62	0	0	0	1	1337
METHYLENE BLUE	1	7	0	43	2	0	0	0	0	0	0	0
NAD_NAD precursors	12	2	0	13	57	1	9	0	0	0	2	9
POLYAMINES	1	2	0	5	0	0	0	0	0	0	0	0
QUERCETIN	2	1	0	13	4	0	0	0	0	0	0	2
RAPAMYCIN	11	0	12	1106	473	0	0	0	0	0	1	1
RESVERATROL	10	5	2	15	10	0	13	1	2	6	1	15
SRT2104	0	0	0	0	0	0	0	0	0	0	2	7
SRT3025	0	0	0	0	0	0	0	0	0	0	0	1
SIMVASTATIN	1	8	0	58	172	0	14	0	1	1	0	42
TRYPTOPHAN	0	2	0	3	9	0	0	0	0	1	0	0
INTERVENTIONS												
CALORIC RESTRICTION	15	7	0	57	20	0	22	3	0	0	0	31
EXERCISE	435	167	0	1214	1979	80	229	331	93	179	121	628
FASTING	20	21	2	281	240	0	50	15	12	22	4	339
KETOGENIC DIET	0	9	0	26	4	0	2	0	0	2	0	7
TOTAL	538	239	20	3496	4141	85	414	357	109	212	134	2564

*Includes age, aging and longevity.

**Includes Alzheimer's disease, dementia and mild cognitive impairment; AD (Alzheimer's disease); CDV (cardiovascular disease); Met.S (metabolic syndrome); Osteoa (osteoarthritis); Osteop (osteoporosis); PD (Parkinson's disease); T2D (type 2 diabetes).