

Belarusian State Medical University

**PHARMACOLOGICAL AND NON-
PHARMACOLOGICAL INTERVENTIONS FOR
AGING**

Department of Pharmacology

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The purpose and objectives

The purpose: to summarize information about pharmacological and non-pharmacological interventions for aging from different literature sources

Objectives:

- Understand potential mechanisms of aging
- Realize possible methods of interventions



Introduction

- Aging is a multi factorial process leading to the loss of physiological function
- It is associated with the development of numerous life threatening diseases such as cancer, cardiovascular diseases and neuro degenerative diseases
- Aging and its diseases cause a huge economic, medical and social burden worldwide
- Hence, development of interventions to slow down aging and the onset of the diseases is necessary



Mechanisms of aging

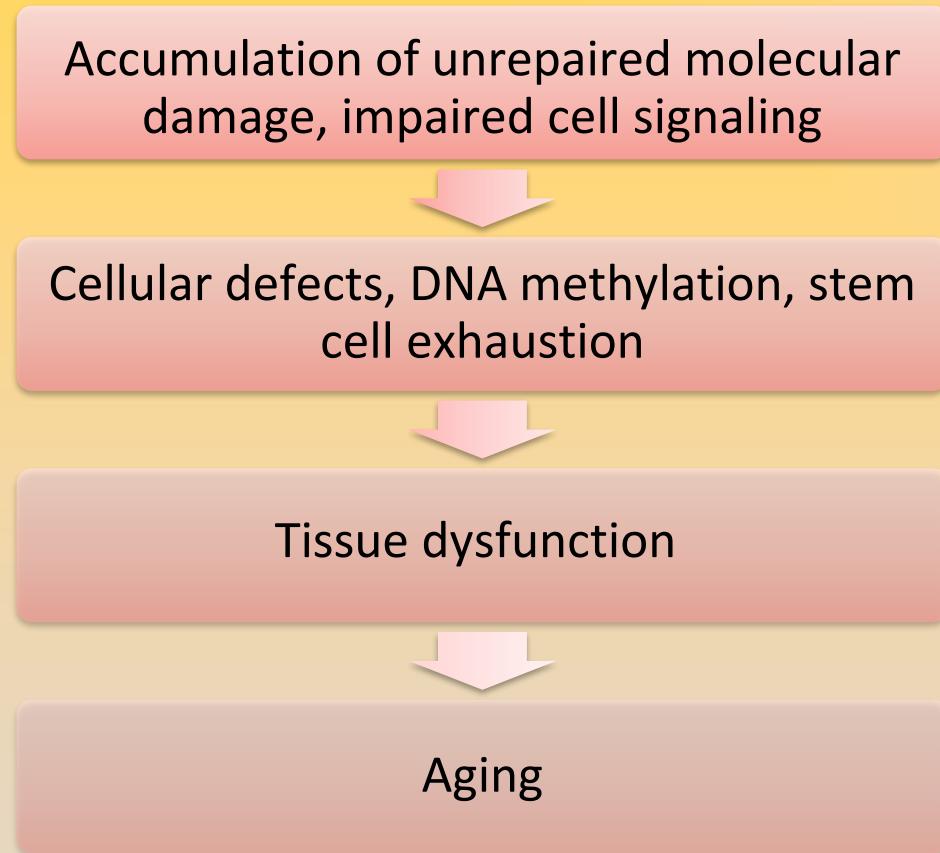


Fig.1. Underlying mechanism of aging

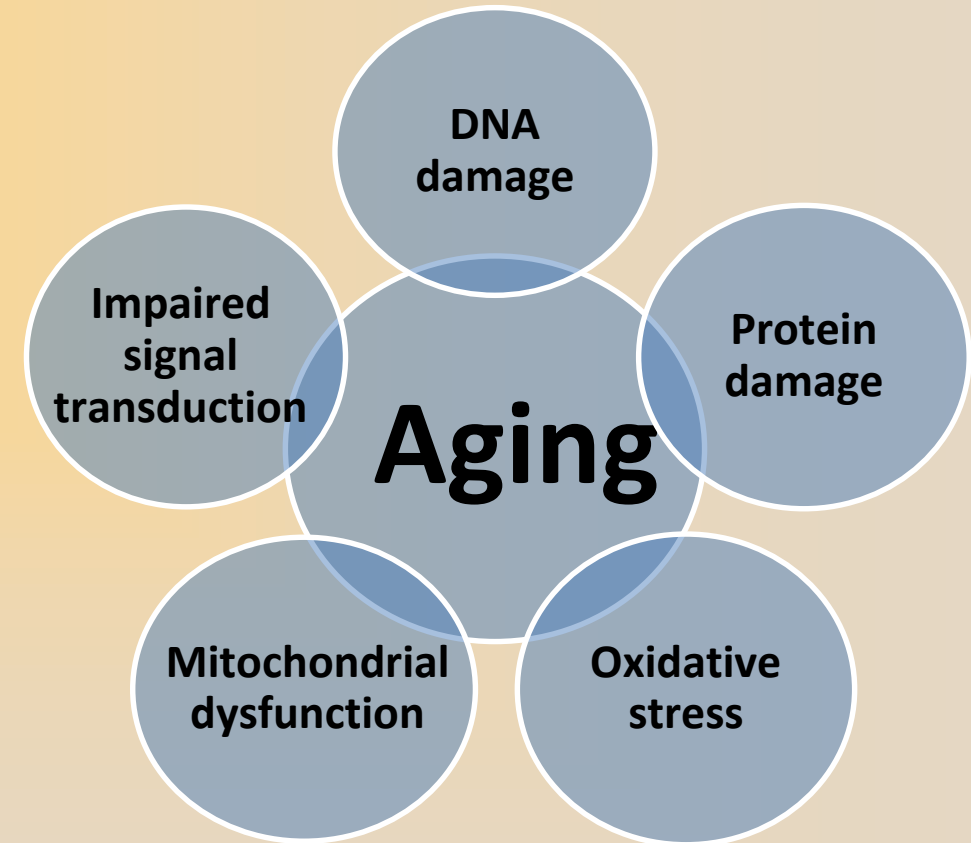


Fig.2. Interaction of various molecular mechanisms that lead to aging

Possible Interventions for aging

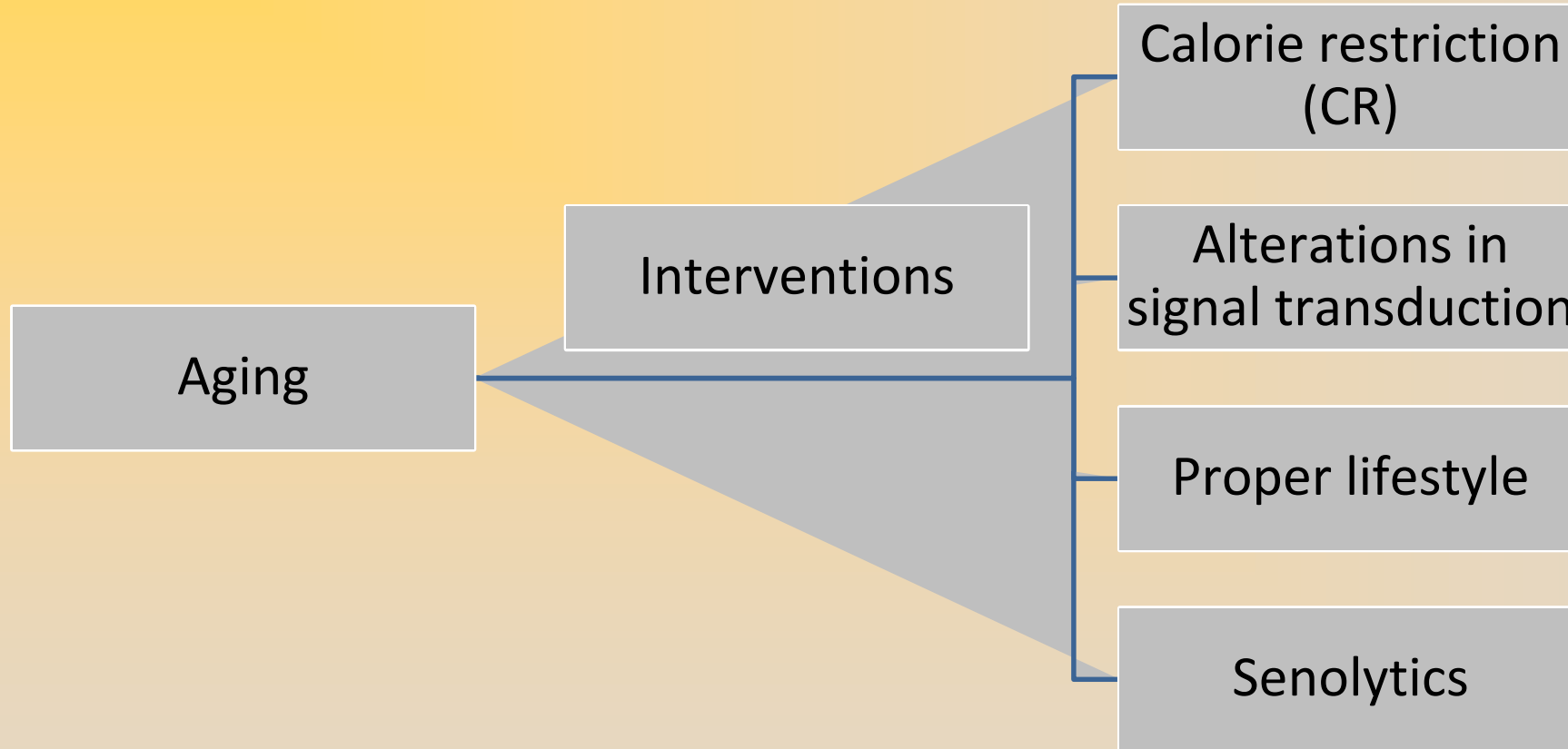


Fig.3. Different interventions to slow aging

Calorie restriction

- A dietary regimen that reduces the daily caloric intake without malnutrition or deprivation of essential nutrients
- One of the most established forms of intervention
- CR counteracts aging by regulating different pathways including:
 - Mechanistic target of rapamycin (mTOR)
 - AMP-activated protein kinase (AMPK)
 - Sirtuins
 - Insulin and insulin like growth factor 1

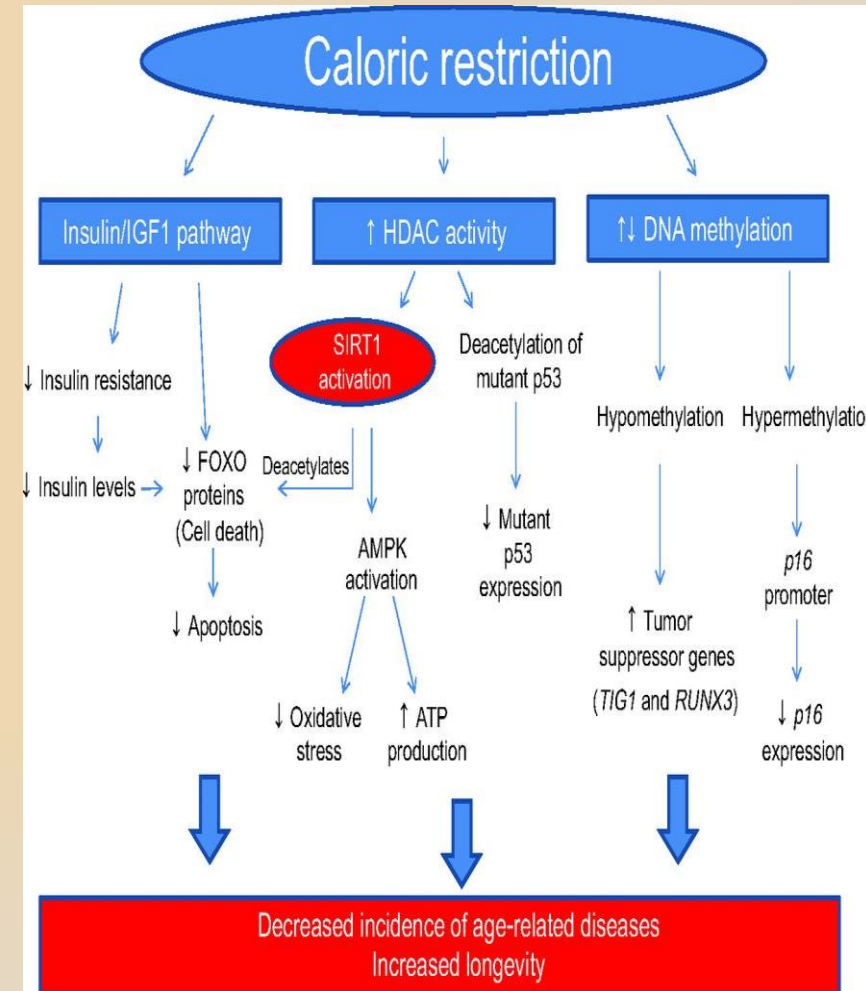


Fig.4. Calorie restriction pathway and its effects

Studies

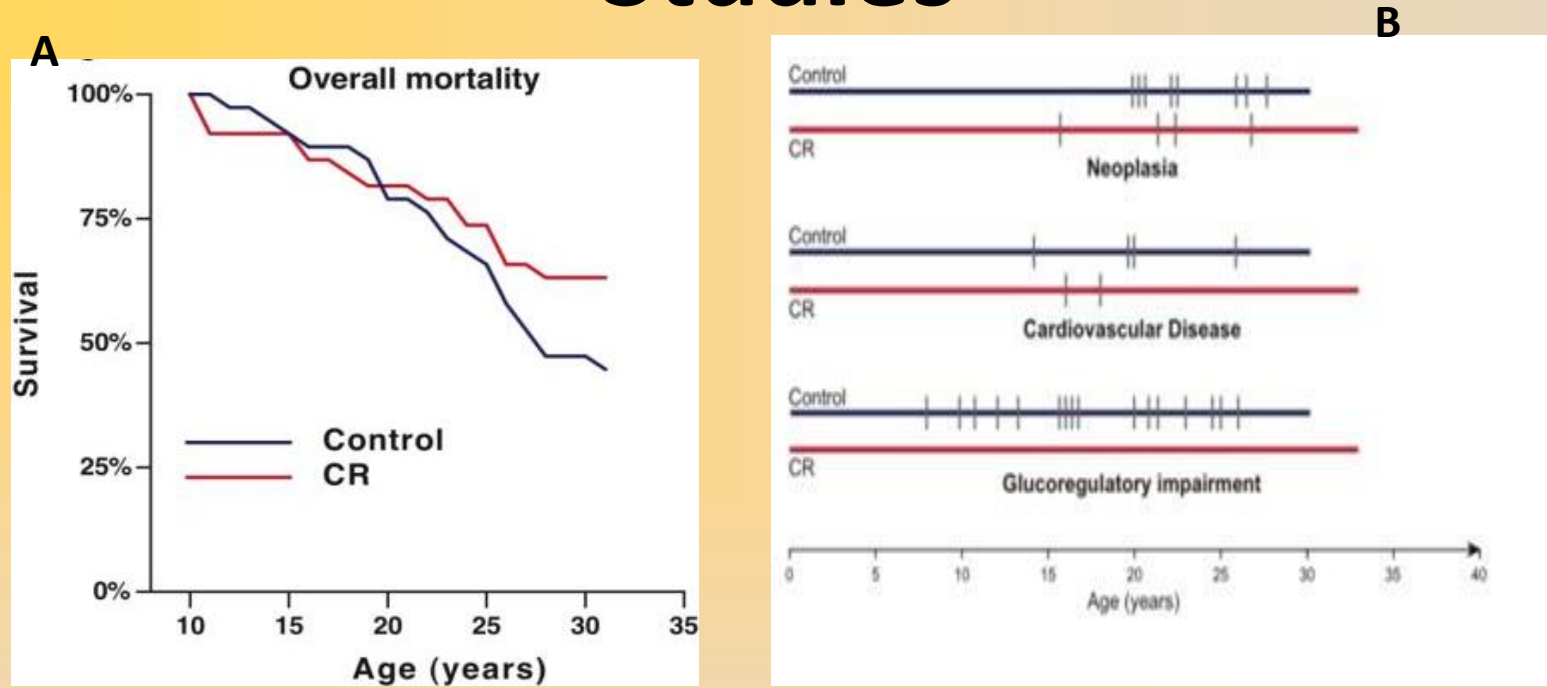


Fig.5. Results from Wisconsin National Primate Research Center

(A) The CR monkeys reported 80% survival rate compared to the 50% seen in the control fed group

(B) Less incidence of age related pathologies compared to the control fed group. Reduced CVD diseases, brain atrophy, diabetes and incidence of cancer were observed in the CR group.

mTOR pathway modulation

- mTOR is a protein kinase which forms the two complexes, mTORC1 and C2
- Regulates cell growth, autophagy, production of protein and energy storage
- Mutations or downregulation of this pathway increased longevity in many animal and yeast models
- **Rapamycin**, a pharmacological inhibitor of mTOR has also increased lifespan due to its inhibition of mTOR pathway

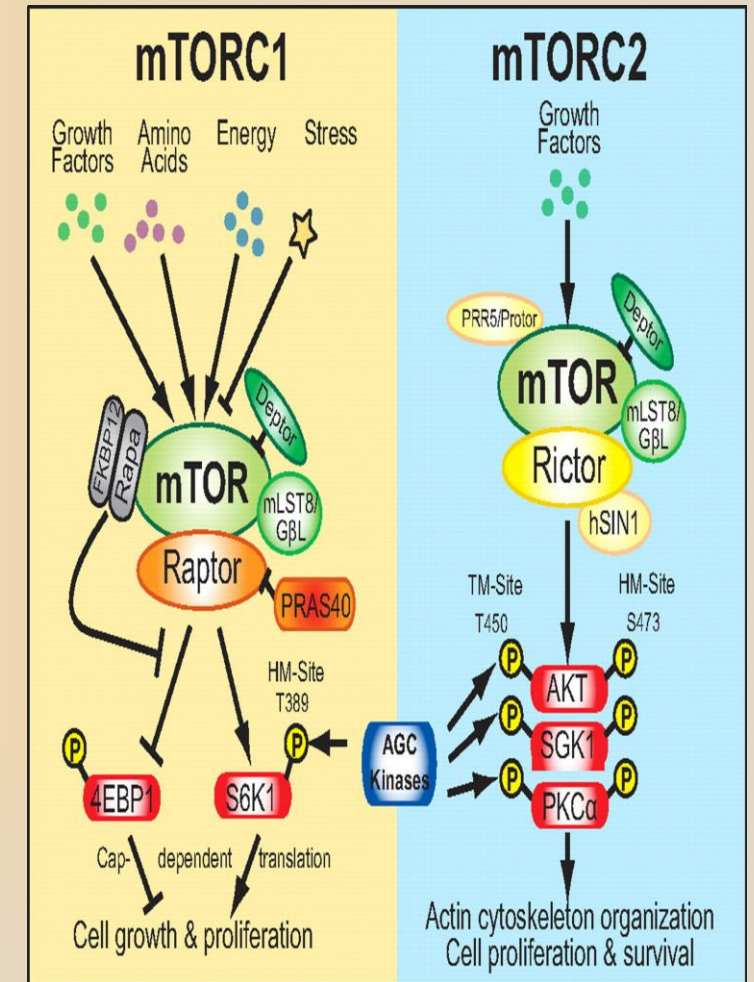


Fig.6. mTOR pathway and its effects

Study	Alteration	Result
Fabrizio et al., 2001	Deletion of gene encoding for S6K in yeast model	Doubling of the yeast lifespan
Jia, Chen and Riddle, 2004	Mutations and RNA interference of mTOR	Extended lifespan in the nematode, <i>C. elegans</i>
Kapahi et al., 2004	Mutation in mTOR in fruit fly and yeast models	Increased life span in both models
Onken et al., 2010	Overexpression of AMPK in nematodes and cancer prone mice using Metformin	Down regulation and impaired mTOR pathway in <i>C. elegans</i> and cancer prone mice
Harrison et al., 2009; Miller et al., 2014	Rapamycin treated mice to disrupt mTOR	Extended lifespan in mice upto 30%
Johnson et al., 2013	Reduced mTOR signaling through genetic and pharmacological interventions	Extended lifespan in yeast, worms, flies and mice

Tab. 1. Overview of some studies carried out in mTOR regulation studies

Insulin/insulin like growth factor signaling modulation

- Insulin and insulin like growth factor 1 (IGF) signaling (IIS) pathway is responsible for energy metabolism and growth.
- Reduced IIS and plasma IGF-1 along with increased insulin sensitivity have increased lifespan in nematodes, fruit flies and mice models

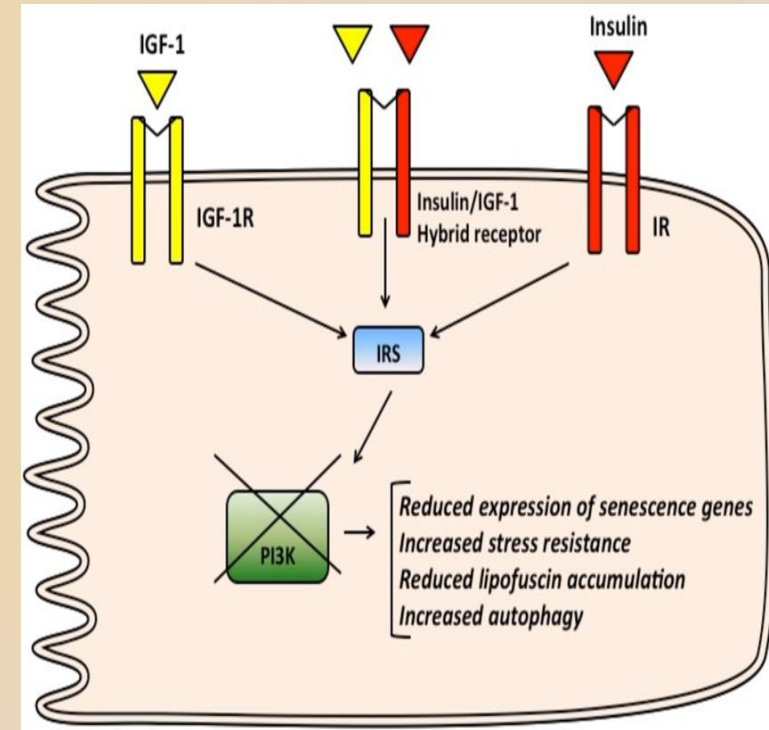


Fig.7. IGF1 modulation effects

Sirtuin pathway activators

- Sirtuins (SIRT1-7) promotes longevity and is capable of mediating many beneficial effects
- Resveratrol, a SIRT1 activator has improved function and extended lifespan in organisms such as *S. cerevisiae*, *C. elegans*, *D. melanogaster*, *N. furzeri* and *A. mellifera* (Hubbard and Sinclair, 2014)
- Additionally, it also showed increased lifespan in mice on a high-fat diet

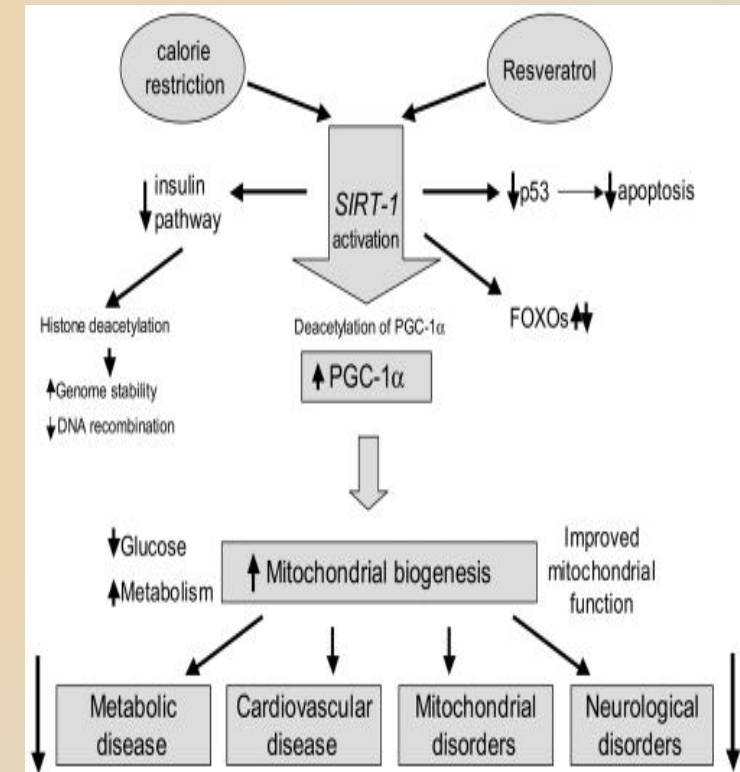


Fig.8. Resveratrol and its effects

Targeting autophagy

- Rate of autophagy declines with age and is a potential cause of several neurodegenerative diseases
- The administration of natural polyimide extended the lifespan of mice and had a cardio protective effect
- Life span was extended up to 25% by lifelong administration of spermidine and also showed reduced liver fibrosis and hepatocellular carcinoma
- Also induced neuronal autophagy thereby decreasing the development of a number of neurological pathologies

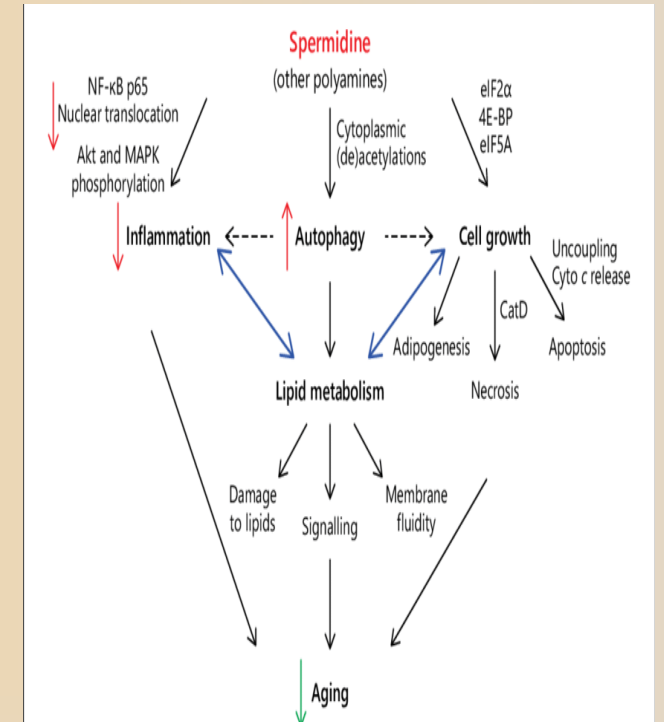


Fig.9. Autophagy targeting pathways

Co-enzyme NAD⁺ boosters

- A decline in the levels of NAD⁺ is observed in aging animal models
- NAD⁺ boosters such as NAD⁺ precursors, synthesis enhancers and inhibitors of NAD⁺ consuming enzymes have shown the ability to extend lifespan of mice
- Thus, NAD⁺ boosters are one of the highly promising drugs to slow aging and improve the quality of life

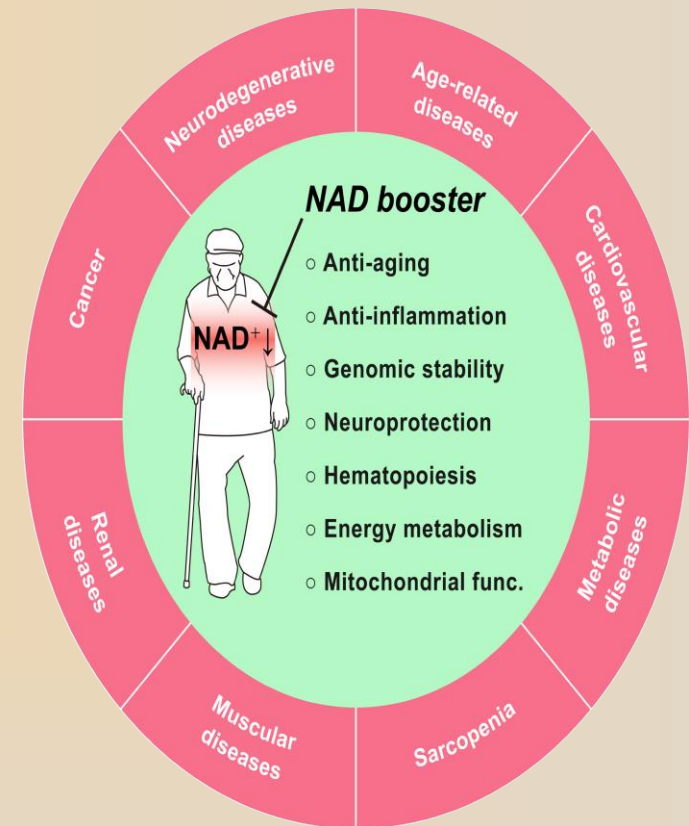


Fig.10. Benefits of NAD⁺ boosters

- The table below summarizes some of the effects of NAD+ boosters seen in aging studies

NAD+ Booster	Effects
Nicotinamide riboside	Rejuvenation of intestinal stem cells and 5% increase in lifespan
NAD+ precursor	A wide range of beneficial effects: improved glucose homeostasis, maintenance of genomic integrity, prevention of heart failure, steatosis and glaucoma
Extracellular nicotinamide phosphoribosyltransferase (eNAMPT)	Extended lifespan in old mice
Nicotinamide and nicotinamide mononucleotide	Improved lifespan and health span in aging models caused due to deficiency of DNA repair

Tab.2. Types of NAD+ boosters and their effects

Senolytic elimination

- Accumulation of senescent cells causes the onset of deterioration and age related diseases
- Treatment with a senolytic cocktail, Dasatinib plus Quercetin alleviated numerous age related features in mice and restored neurogenesis
- Furthermore, the senolytic AP20187 extended the median lifespan of mice by about 25% and prevented bone deteriorations in aging mice
- Nevertheless, the safety and efficacy of these drugs should be well evaluated before introducing as an anti-aging treatment for humans

Proper lifestyle

- Diet, physical activity, alcohol intake and smoking plays a major role in health as well as in the development of many diseases
- Regular exercises along with reduced intake of alcohol, sugar and saturated fats have increased lifespan by two or more years
- Furthermore , the adaptation of a Mediterranean diet has shown countless benefits such as increased longevity, improved cognition in elderly, prevention or slowing down of metabolic syndromes
- Inclusion of antioxidant rich food has been shown to reduce oxidative stress and inflammation and has a protective action against free radicals and DNA damage

A



B



Fig.11. Diet (A) and exercise (B)

Conclusion

- Main strategies to prolong lifespan include:
 - Dietary interventions
 - Proper lifestyle
- Promising interventions, that could slow down aging is:
 - Drugs that inhibit GH/IGF-1 axis
 - Drugs that inhibit mTOR-S6K pathway
 - Drugs that activate AMPK or specific sirtuins
 - NAD+ boosters
 - Senolytics



THANK YOU