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Recent Advances: Anti-Ageing Drugs- A review

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Abstract:

It has been a very ancient will of man to find cure of chronic disordered condition called as 'ageing'. Ageing itself leads to various age related diseases including cancer. If somehow ageing process stopped or delayed this defective condition can be avoided. After intense prolong research caloric restriction found to be fully effective against ageing .Surprisingly, the most effective interventions proposed to date converge on only a few cellular processes, in particular nutrient signaling, mitochondrial efficiency and autophagy. In this review we are trying to give idea about recently developed different types of anti-aging drugs.

Keywords: Resveratrol, antiaging drugs, life prolongation, Sirtuins, Caloric restriction.

Introduction:

Aging is the single most important risk factor in the development of many diseases, such as cancer, cardiovascular disorders, neurodegenerative diseases, osteoporosis, and metabolic disorders.[1] Improvements in health care have increased human life expectancy in recent decades, and the elderly population also brought increased years of poor health or disability.[2] By one measure, nearly one-half (45%) of India's disease burden is projected to be borne by older adults in 2030.[3] So not only increase in life span but also improvement in health span is major challenge and after over years of research new developing anti-aging drugs look promising. Anti-aging most effective interventions proposed to date converge on only a few cellular processes, in particular nutrient signaling, mitochondrial efficiency, proteostasis and autophag.[4]

Aim of the present study is to review recent advances in different classes of anti-aging drugs with therapeutic aspect.

Material and Methods:

Relevant article were identified through PUBMED and GOOGLE SCHOLAR search using terms: anti-aging, life prolongation, Sirt-1, caloric restriction. Review article and meta-analysis were also used.

Mechanism of Anti-ageing drugs:

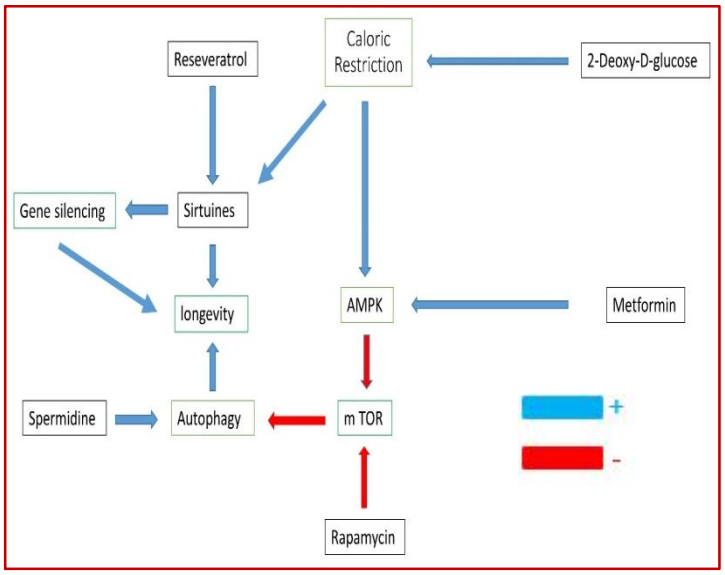

Figure 1. Caloric Restriction and action of Anti-aging drugs.

Resveratrol activates sirtuines and inhibit mTOR which promot autophagy. Metformin mainly act through AMPK (adenosine monophosphate activated protein kinase) pathway. Spermidin exert effect via autophagy dependent antigenic mechanism. Rapamycin inhibit mTOR indirectly help in autophagy. Ingestion 2-Deoxy-D-Glucose can mimic Caloric restriction like condition.

Currently established drugs –

Traditional anti-ageing drugs contain typically anti-oxidative compounds like Vitamin C, vitamin E[5], superoxide dismutase[6] (SOD). Unfortunately taking SOD tablets has no effect on cellular ageing; the enzyme is simply broken down in the body during digestion. And when antioxidant vitamins are added to cells they compensated by halting production of their own antioxidants, leaving free radical levels unchanged.[6] Also mounting evidence from a multitude of species indicating that there is no direct relationship between reactive oxygen species (ROS) and longevity.[7]

Recent anti –aging drugs-

Resveratrol - A polyphenol that is found in grapes and in red wine. Overall, it is clear that resveratrol treatment or SIRT1 over expression prevents several age-associated diseases and pathogenic conditions, including oxidative stress in the aging heart, neurodegeneration or DM.[4]

Quercetin - Present in many fruits and vegetables .when quercetin supplemented to already senescent fibroblasts, a rejuvenating effect was observed .Also, possesses anti- oxidant properties reducing lipid peroxidation products and increasing glutathione levels in the mouse brain.[2]

SRT1720 - A synthetic compound, activate Sirt1 in vitro, extends both mean and maximum lifespan of adult mice fed a high-fat diet. This lifespan extension is accompanied by health benefits including reduced liver steatosis, increased insulin sensitivity, enhanced locomotor activity and normalization of gene expression profiles and markers of inflammation and apoptosis, all in the absence of any observable toxicity.[8]

SRT2104 - A novel, first-in-class, highly selective small molecule activator of the NAD + dependent deacetylase SIRT1 series of phase 1 showed good tolerability of all doses demonstrated in these studies.[9]

Melatonin- Strong antioxidant capacity, melatonin may be a safe and effective remedy to slow down aging, extent the life span and counteract age-related disorders such as Alzheimer's and Parkinson's diseases .Also reduced the incidence of carcinogenesis in the colon, mammary gland and uterine cervix.[10]

Rapamycin- An inhibitor of the TOR kinase, is a natural product Secreted by a soil bacterium. It is interesting that intermittent rapamycin feeding opens up new opportunities to avoid immune-suppression and its potentially detrimental effects on lifespan extension.[4]

Spermidine- A naturally occurring polyamine induces autophagy. Endogenous spermidine concentrations decrease as the organism age.

Chronic spermidine feeding promotes increase in health span in mice.[4,11]

Metformin- The most prescribed drug for the treatment of Type-2 diabetes. It is a potent, indirect activator of AMPK, increase of the AMP/ATP ratio, thereby inhibiting mTOR, a protein kinase involved in the control of cellular proliferation and tumor growth.[4]

2-Deoxy-d-Glucose- Inhibition of glycolysis induce cellular reactions similar to CR .The glucose analogue, 2DG is a promising candidate, since it is taken up by cells and, being not further metabolizable, competitively inhibits glucose utilization.[2]

TA 65 - small-molecule activator of telomerase (TA-65) purified from the root of Astragals membranaceus is capable of increasing average telomere length and decreasing the percentage of critically short telomeres. Dietary supplementation in female mice leads to an improvement of certain health-span indicators including glucose tolerance, osteoporosis and skin fitness[12] but not much data available efficiency and safety is question mark.

Group		Drug and dose	Mechanism	Adverse effect	Status	Increase % longevity
Calorie Restriction Mimetics (CRM):						
Sirtuin 1 Activating Compunds (STACS)	**Resveratrol and other Polyphenolic STACS**	**Resveratrol** 30-450mg/day (oral)[13]	SIRT-1 activator	Nausea, GI discomfort (human)[4]		*Yeast - 70% [2]
		Quercetin 800 mg to 1200 mg/daily(oral).[5]	Increases SIRT-1	High dose renal and cardiovascular toxicity[14]	Phase I[14]	*Yeast - 60%[15] C.elegans - 11% to 16% [2]
	Non polypheolic STACS	**SRT1720** 30mg/kg-100mg/kg(oral)[8]	Indirect SIRT-1 activator	No apparent side effects and toxicity[8]		Mice - 3% and 5% [8]
		SRT2104 0.03 - 3.0 g (oral) or 100 mg(I.V.) [9]	Indirect SIRT-1 activator	Headache, flatulence nausea[9]	Phase I[9]	Mice - mean and maximal lifespan
****Indirect Activator of AMPK**	**Biguanides**	**Metformin** 150 -300 mg/kg (oral)[16]	***Insulin reduction and mTOR inhibition[16]	Cause malabsorption of vitamin B12		C.elegans - 26.1% mice -10%[16]
Effects on energy metabolism		**2-Deoxy-D-glucose (DOG)** 45 mg/kg (oral)[17]	lowering cellular energy production	long-term treatment proved to be cardiotoxic[2]	Phase I	C.elegans –increase lifespan
Other Molecules:						
M tor inhibitor		**Rapamycin** 0.5mg/kg(oral) intermittent[2]	Block mTOR	Immunosuppresion		Male and female mice - 9% and 14% [3]

Autophagy regulator molecule	**Spermidine** <83 mg/kg[18]	Triggers autophagy	Decreased plasma calcium and inorganic phosphate[18]		Yeast, nematodes and flies, mice prolongs the lifespan[19]
Hormone	**Melatonin** 2 - 20 mg/l(drinking water of mice)[20]	Mitochondrial modulation sirt1activator [21]	No harmful effect[10]		Rats - 10% [20]

Conclusion:

Caloric Restriction mimetic drugs look promising in anti-aging therapy. New developing artificial compound are more potent in induce CR like condition, more safe with good tolerability. Poly phenols, the naturally occurring compound show additional antioxidant activity with Sirt1 activation preferable over traditional anti oxidative compounds. Autophagy induction and energy conserving pathway seem new way to prolong life span effectively. Telomerase related drug need more research. Overall new developing anti- aging drugs have potential to change the future.

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