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# TREATING AGEING: A REVIEW

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**ABSTRACT:** Natural lifespan is as long as it is necessary to allow an organism to reproduce, and die accidentally. In nature, no animal lives to old age. Among humans and domesticated animals, ageing is a natural progression in life. According to gerontology, non-repaired molecular damage and accumulation of reactive oxygen species (ROS) cause ageing. Knowing ageing pathology means that there are now ways to manage molecular damage and slow down or limit ageing, pharmacologically. TOR is a conserved kinase that regulates cell growth and metabolism in response to environmental cues. In the post-development and post-reproduction period of the human lifespan, TOR accelerates disease and ageing. It has been seen that many well-known established drugs already in use can inhibit the TOR pathway and can slow down ageing as well as prevent or ameliorate age related diseases. Whether ageing should be treated pharmacologically or not may still be debated, but the availability of drugs means that we need to address the issue of ageing management sensibly, ethically and equitably.

**Keywords:** ageing, senescence, rapalogs, anti-ageing, lifespan, TOR pathway.

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## 1. INTRODUCTION

Can we treat Ageing? Should we?

The World health organization (WHO) states that in 2019, the number of people aged 60 years and older was 1 billion worldwide. It is predicted that the number of elderly will increase to 1.4 billion by 2030 and 2.1 billion by 2050. [1] In the natural world, from the point of view of evolution,

senescence or getting old (and death) is predictable. In a natural environment, an animal has a little chance to survive above a certain age, because death can result from a multitude of external factors like predators, competition for food, constantly changing pathogens and environmental changes and disasters. Natural lifespan is as long as it is necessary to allow an organism to reproduce, and then die accidentally. For most populations in nature, mortality occurs well before 'old age'. However, in more controlled environments, humans, domesticated and laboratory animals die from senescence. Unfortunately, living longer requires quid pro quo with other factors. For example, the female species that have no ovaries would not develop ovarian cancer and would live longer but would not be able to reproduce. Hence, mutations that prolong life but interfere with development are eliminated within a generation. So a longer lifespan is not an evolutionary choice. [2] However, human nature is insatiable, and as technology and knowledge about the human body grows exponentially, and pharmacological interventions move away from disease management to health promotion, we need to address the problem of ageing in a different way than it was looked upon in classical gerontology, when ageing was inevitable and age related diseases were a part of the natural progression of life.

## SEARCH STRATEGY AND SELECTION CRITERIA

My search base was PubMed, Google Scholar, SCOPUS, and Web of Science for full-text articles published from database inception to November, 2024.

Articles included in this review met the following criteria: ageing-related physiological and pathological changes of disease were detailed; pharmacology of drugs used was explained fully, ethical issues were discussed, and the articles were published in English.

## THEORIES OF THE PATHOLOGY OF AGEING AND THE HUMAN LIFESPAN

How long can we live naturally?

### Hayflick limit:

One popular theory that explains ageing is the "Hayflick limit." In 1965, Hayflick studied fibroblasts in vitro and found that they have a limited lifespan; they can replicate about 50 times in cell culture and then they go into irreversible cycle arrest (senescence). The Hayflick limit is depends on the amount of telomere shortening during each cycle of fibroblast cell division. Still, the Hayflick limit is not universal. Many cells in the body do not proliferate regularly and therefore do not lose telomere length. [3]

### ROS action:

Another theory of ageing is the accumulation of ROS (reactive oxygen species) or free radicals that cause random damage to the cell and DNA. Natural anti-oxidants, both endogenous (produced in the body) and exogenous (from our diet and lifestyle) usually neutralize the ROS, but damage accumulates over the years, leading to cell ageing and apoptosis. However, random damage would result in random diseases. But human ageing is very similar: skin wrinkles, male baldness,

osteoporosis, hypertension, atherosclerosis, obesity, diabetes, Alzheimer's disease and cancer. Therefore, ROS accumulation is only partially correct as a theory of ageing. Also, preventing ROS damage by using antioxidant supplements has not revealed any evidence of increase in life span. [4]

**Hormesis:**

The opposite theory (known as "hormesis") is that small and repeated stress can stimulate the cellular "intrinsic capacity for self-maintenance and repair." It is suggested that ROS production can induce antioxidants and DNA repair. Intermittent fasting is a good example, where calorie restriction has proven beneficial effects on blood pressure, glucose metabolism and inflammation. [4] Because of the hormesis theory, various nutraceutical agents that can mimic hormesis in the body are now being developed. Bimoclomol, and celastrol, two heat-shock proteins, paired with a protein-protective cover and are now being tested for cyto-protective action. Curcumin, an Indian yellow spice, has long been shown to have cyto-protective effects through its hormetic action. Some chemical mimetics of caloric restriction, such as 2-deoxy-D-glucose and its analogues, and resveratrol, a polyphenol, are also being investigated for their use as anti-ageing hermetic agents. (5) Unfortunately, effective hormesis can also cause cancer, by selecting for oncogenic mutations that sustain endless cell division, finally killing off the whole person. So, what is good for a cell may not be good for the whole organism. [4]

**Hypertrophy:**

Another theory of ageing is 'hypertrophy and hyper-proliferation.' According to this theory, senescence is a quasi- program of development that has not been turned off. Initial hyper-function leads to secondary decline when hypertrophied or hyper-proliferated cells do not function as they should. In humans, age-related changes are seen as accumulation of fat (obesity and atherosclerosis), increased in blood pressure and glucose, increased stickiness of platelets, cellular hyperplasia and hypertrophy (manifested as benign tumors). Age related changes in men like male baldness and enlarged prostate are caused by excessive androgen stimulation. There is no decrease in blood cell production or in epithelial cell renewal. Old animals do not die from anemia or thrombocytopenia. In fact, old age can lead to different types of leukemia due to mutations that cause over-proliferation of cells. Osteoporosis, which can lead to fractures, results from hyper-function of osteoclasts, cells that resorb bones. Liver grafts from the elderly can be transplanted with ease, indicating that the liver does not age. Finally, nutrients and hormone supplements do not slow down ageing. [4]

**Epigenetic alterations:**

Epigenetic mechanisms like DNA methylation, post-translational modification of histones and chromatin remodeling are driven by exogenous (e.g., environmental toxins) and endogenous (e.g., hormonal) factors, which lead to changes in gene transcription and translate to abnormal proteins that can cause cellular malfunction and ageing. [5]

**Loss of proteostasis:**

We know that accumulation of misfolded proteins contributes to age-related diseases like Alzheimer's disease and Parkinson's disease. Promotion of proteostasis, the process that regulates protein homeostasis, might benefit these conditions.

The heat shock family of proteins restores or degrades misfolded/abnormal proteins. Studies have shown that the up-regulation of heat-shock proteins promotes lifespan. [6]

**Sirtuins and ageing:**

Silencing information regulator 2 related enzyme 1(Sirtuin1, SIRT1) is an NAD+-dependent deacetylase, involved in the regulation of cellular senescence and ageing. Overexpression of mammalian sirtuin family of proteins, including SIRT1 and SIRT6 (regulates genomic stability), and SIRT3 (response to dietary restriction) causes histone modification, which contributes to genetic transcriptional regulation to promote healthy ageing or the opposite. Decrease in SIRT action in cells have therefore been linked to a large number of ageing-related diseases like atherosclerosis, chronic kidney diseases, chronic obstructive pulmonary disease, and neurodegenerative disorders like Alzheimer's. [6]

**NAD+:**

Ageing is associated with a gradual decrease in tissue and cellular NAD+ (oxidized form of NAD) levels. This decline in NAD+ levels is linked to many of the ageing-related diseases. SIRTs are NAD+-dependent and regulate many longevity-related biological processes such as DNA repair, autophagy, inflammation, protection against oxidative stress, and metabolism. [6]

**Growth hormone and IGF 1:**

Growth hormone, insulin and insulin-like growth factor 1 (IGF-1), share the same signaling pathway. Malfunctions of GH, IGF-1 receptor, insulin receptor can affect lifespan via their signaling molecules, like AKT and mTOR within the cell. In humans, genetic variations that cause reduced insulin/IGF-1 signaling are associated with longevity. One striking characteristic of centenarians is their greatly increased sensitivity to insulin and also a reduced adipose tissue mass. TOR phosphorylates IRS-1 (Insulin receptor substrate 1), leading to impaired insulin signaling. Therefore, insulin resistance is a marker of hyperactive TOR. And, decrease in IGF-I/insulin signaling decreases TOR activity and slows down ageing. [7]

**Mitochondrial dysfunction:**

The presence of mutation in the mitochondrial genome (mtDNA) especially in ageing cells is a very common feature due to the low capability of DNA mutation repair in mitochondria. Mitochondrial dysfunction is one of the main causes of cellular ageing. Ageing cells with mtDNA mutation might contribute to the development of cancer as well. [7]

**Altered intercellular communication:**

In any multicellular organism, cells communicate with each other to ensure proper functioning of

the organism. Cells communicate in two ways; electrical or chemical synapses. Changes in these communication signals slowly and continuously increase with age. There are four main methods of change.

- Inflammageing is a slow, sterile, low-grade inflammation that develops with ageing through the activation of inflammasomes, an intracellular multi-protein. It is characterized by elevated blood inflammatory markers like ESR and CRP.
- Immunosenescence is the deterioration of immune functions due to ageing and leads to the susceptibility of the elderly to infection, autoimmune disease and cancer.
- Neuroendocrine dysfunction happens due to decrease in neurotransmitters and hormones secretion by the autonomic nervous and endocrine systems, leading to age-related diseases and reduced lifespan.
- Bystander effect is an entity where age-related disorders in one tissue induces the same disorders in neighbouring tissues, like AMPK activation or mTOR inhibition, causing genomic instability and apoptosis. [7]

**CDK inhibitors:**

Cell senescence and decrease in replication is mediated by CDK inhibitors (located on genes p21 and p16). Any stimuli that induce CDK inhibitors can result in cell senescence. [7]

**Dis-regulated nutrient sensing:**

mTOR is a protein kinase responsible for environmental nutrient sensing, and controls cellular metabolism, immune response, autophagy, cell survival and proliferation, and maintains cellular homeostasis. mTOR catalyzes the phosphorylation of several critical proteins in the cell, like AKT, protein kinase C, insulin growth factor receptor (IGF-1R), ribosomal protein S6 kinase (S6K), transcription factors, binding proteins, and autophagy-activating kinases. Disorder of mTOR regulation is linked with several degenerative and lifestyle diseases like aging, arthritis, insulin resistance, osteoporosis, cancers, and neurological disorders. [8] DNA damaging agents all activate the TOR kinase. TOR accelerates disease and ageing. [9] Hyper-stimulation of TOR (by nutrients) promotes obesity. Thus, the complex metabolic syndrome can be explained by a single cause: hyper-activation of TOR. Conversely, reducing TOR action will cure diabetes and obesity. Cellular hyperfunction, hyperplasia and hypertrophy contribute to atherosclerosis and hypertension, which in turn lead to strokes and myocardial infarctions. Hypertrophic stimuli, such as angiotensin II, can activate protein synthesis via the TOR pathway. Also, TOR inhibition decreases established cardiac hypertrophy, improves cardiac function and suppresses experimental aortic aneurysm. [2] Multinucleated bone-resorbing osteoclasts are cells of hematopoietic origin that play a major role in osteoporosis. Osteoclasts survival and activity require cytokines, which all converge on TOR and thus exert anti-apoptotic action.

Activation of the TOR pathway leads to Alzheimer's disease, Huntington's disease (HD) and mutant tau in fronto-temporal dementia. TOR can increase Tau protein and TOR activation causes neurodegeneration. Age-related macular degeneration (AMD), a leading cause of blindness in the elderly is associated with accumulation of amyloid (like in other neurodegenerative disorders) and neovascularization from increased secretion of IGF-I and VEGF. All these factors are TOR-dependent. If we pharmacologically switch off the TOR-driven program, it may prolong life; and this may even reveal new causes for death. [2]

**IMPACT OF SENESCENCE ON HUMAN HEALTH**

Persistent ageing cells in the adult are produced in at least three different contexts related to human health:

- normal ageing,
- age-related disease and
- therapeutic interventions

In normal 'healthy' ageing, tissue dysfunction still occurs with senescence, but specific age-related diseases occur only in some. When there are many senescent cells, disease might emerge due to additional stressors acting on a vulnerable senescent cell, like an insulin-resistant fat cell confronted with a high-fat diet; or a DNA-damaging agents in cigarette smoke, or simply telomere erosion. [10] So, do we diagnose ageing itself as a disease, or look at the effects of ageing on human health and cure those? It has been seen that even if we cured all the big killers that occur with age (heart disease, cancer, and stroke) average life expectancy in the population would only rise 12 years or so (from 77 to 89 in the United States). This is because once we save a person of dying from one disease, they die of another disease. [4] The major assumption behind research on ageing is that age-associated diseases may be regarded as a pathophysiological phenomenon of the same disease process (senescence) that can be treated or even prevented. The field of ageing management has been successful due to the application of 'omics'-based research, such as genomics, transcriptomics, proteomics and metabolomics, leading to a better understanding of cellular pathways involved in the ageing process. Thus the improved knowledge about inflammation, autophagy, mitochondrial efficiency and nutrient signaling and has led to effective interventions for treating and reversing ageing. To think of ageing as a disease becomes the strategy for "anti-ageing medicine" as well as an agenda for legitimate research in bio-gerontology.

**DIAGNOSING AGEING**

Senescent cells are characterized by a collection of basic features like growth arrest, expression of anti-proliferative molecules, and activation of damage sensing signaling pathways. Although aged cells are non-replicative, they are metabolically active and often capable of performing the same functions of the replication-competent cells from which they derive. [11]

The biomarkers of ageing are varied.

a) Physiological markers like gait speed, grip strength, heart rate variability, and blood pressure.
b) Blood based biomarkers are fasting insulin levels, IGF1, HbA1c, Interleukin-6, TNF alpha, HsCRP, Cystatin C.
c) Neurological assessments like vision, hearing and mini-mental state exam.
d) AI driven age prediction is gaining popularity with tests such as DNA methylation, metabolomics, proteomics, microbiome analysis and retinal scans. [10]

**ANTI-AGEING DRUGS**

Unfortunately, clinical trials for anti-ageing drugs will require a lifetime to determine. This can be particularly challenging unless such a drug is already in clinical use for a different indication.

Criteria for potential anti-ageing drugs are:

1. Drugs that prolong life span in study organisms.
2. Drugs that prevent or delay several age-related diseases.
3. Drug that suppresses cellular senescence

According to all 3 criteria, rapamycin and other rapalogs are the ultimate anti-ageing drugs. [7]

**TOR Inhibition via Rapalogs: Rapamycin (Sirolimus/Rapamune) and Everolimus**

Rapamycin (also known as sirolimus) is an immunosuppressive agent that acts as an mTOR inhibitor and has been used for the prevention of organ transplant rejection for over 30 years. But rapamycin has also been shown to produce anti-ageing effects in experimental animals such as mice and fruit flies. [7] Rapamycin transforms the immunity from aged-type to infant-type, resulting in the induction of immunologic tolerance to transplantation. In adults, rapamycin prevents transplant rejections, whereas in infants, transplantation is possible without rapamycin. Thus rapamycin eliminates hyper-immunity but does not suppress immunity completely. It can therefore be used for the therapy of certain infections such as invasive fungal and HIV infections. Rapamycin is used as an anti-cancer drug as well. Cancers with hyperactivation of the TOR pathway due to genetic mutations are hyper-sensitive to rapamycin. It also inhibits angiogenesis in cancer patients. In addition, rapamycin may be useful in the treatment of psoriasis and other inflammatory dermatoses. Data suggest that rapamycin could also be used for prevention of atherosclerosis, hypertension and hyper-coagulation (prevention of myocardial infarction and stroke), autoimmune diseases and arthritis, obesity, type II diabetes, nephropathy, macular degeneration, multiple sclerosis, Alzheimer's and Parkinson's diseases, and osteoporosis. Rapamycin's safety profile is already well known since it has been administrated daily to transplant patients for several years. Its pharmacokinetics has been studied in healthy volunteers as well. Rapamycin acts as an anti-ageing drug by preventing diseases rather than curing any complications of diseases. Rapamycin may prevent damage but not to reverse it. Cumulative studies by 2006 already suggested that rapamycin can act as a universal anti-ageing drug – that is, it extended lifespan in all tested models from yeast

to mammals, suppressed cell ageing and delayed the onset of age-related diseases. [12] Please note, self-medication (even by physicians themselves) should be avoided and strongly discouraged. Side effects: The use of rapamycin and its derivatives by organ transplant recipients and patients with cancer is known to be associated with adverse events including systemic infections, mouth ulcers, headache, fever, nausea, abdominal pain, constipation, diarrhoea, peripheral oedema, anaemia, arthralgia, thrombocytopenia, hypercholesterolaemia, hypertriglyceridaemia, increased creatinine and hypertension. [13] In healthy individuals, although no serious adverse events were attributed to treatment with rapamycin or its derivatives, it is important to note that only single doses of rapamycin or its derivatives were administered in the studies and is insufficient to confirm long-term safety. Five deaths due to serious adverse events, probably related to everolimus, occurred in one study of postmenopausal women with breast cancer treated with everolimus and exemestane daily for 48 weeks. The causes of death were bilateral pneumonia, and disease progression. In another study, treatment related adverse events resulted in permanent everolimus discontinuation in 33% of individuals aged 65 years or older and 17% of those younger than 65 years. [13]

**Metformin:**

Metformin, one of prescribed drugs for type 2 diabetes mellitus, activates LKB1 and AMPK (adenosine monophosphate protein kinase). AMPK inhibits TOR. Thus, metformin inhibits TOR indirectly. Inhibition of TOR restores insulin sensitivity and therefore reduces blood sugar. The mechanism of action of metformin through LKB1/TOR pathways was understood just recently. Metformin acts through inhibition of mTOR, reduction of endogenous production of reactive oxygen species (ROS), and reduction in DNA damage. Hence it can not only reduce hepatic glucose production (through decreased gluconeogenesis), but it may also suppress lipid synthesis. [14] Metformin treatment may produce various health benefits, including the reduced risk of cardiovascular disease and cancer, improved cognitive function in the elderly, prolonged survival in patients with diabetes, and an extended lifespan. In 2016, metformin was first used as an anti-ageing drug in a clinical trial, the Targeting Ageing with Metformin (TAME) program because of its potential lifespan-extension effects. [15]

**Resveratrol**:

Resveratrol (trans-3,4,5'-Trihydroxystibene) is the most popular experimental therapeutic life extension supplement. It first attracted attention when it was postulated to explain the cardio-protective effects of red wine. Resveratrol, initially identified as a polyphenol from a flowering plant, is a potent natural SIRT1 activator. It can be found in red wine, grape skins, and peanuts and it has been shown to be able to promote longevity across species. Resveratrol has protective effects in metabolic syndrome, type 2 diabetes, neurodegenerative disorders, and cardiovascular disease mostly through activation of SIRT1 and subsequent prevention of oxidative stress, apoptosis, and inflammation. [6] Just like rapamycin is produced by bacteria to inhibit fungal growth, resveratrol

is produced by plants to inhibit fungal growth too. In humans, resveratrol also suppresses angiotensin II-induced kinase phosphorylation and subsequent hypertrophy in rat aortic smooth muscle cells and inhibits of IGF1. [2] Studies have shown that resveratrol mimics effects of dietary restriction (DR) in lower organisms. In mice, resveratrol-fed elderly mice show a marked reduction in signs of ageing, like reduced albuminuria, decreased inflammation and apoptosis in the vascular endothelium, increased aortic elasticity, reduced cataract formation, and preservation of bone mineral density. However, young mice did not live longer when treated with resveratrol. Unfortunately, in humans cardiovascular disease is a big cause mortality and morbidity, unlike in mice; therefore a DR mimetic such as resveratrol could have a greater impact on humans. [16]

**Curcumin:**

This antioxidant compound is the natural polyphenol of turmeric. Many evidence-based studies prove the anti-oxidative, anti-carcinogenic and anti-inflammatory effects of curcumin. Unfortunately, it is poorly absorbed from the intestines. Besides, its structural instability, limited penetration of the blood–brain barrier and rapid degradation in the body limit its potential as a therapeutic agent. Therefore, studies are investigating modifying the curcumin structure to improve bioavailability without compromising its protective properties. Studies are ongoing to improve bioavailability by conjugating curcumin with lipids, encapsulating curcumin in a nanoparticle, constructing complexes with manganese or co-treating curcumin with piperine. [17]

**Carnitine:**

Carnitine is one of the substances found in human tissue used to transport long-chain fatty acids into mitochondria for energy production and excrete excess organic substances. Carnitine is also a lysine and methionine derivative that plays as a free radical scavenger.

All these mechanisms turn out to extend lifespan.

**Statins:**

Statins are used to treat dyslipidemia and prevent cardiovascular disease in high-risk patients. Statins lower serum lipid by competitively blocking at active sites of HMG-CoA reductase, which converts HMG-CoA to mevalonic acid, and leads to reduced hepatic cholesterol synthesis. Besides lowering lipid synthesis, statins have an anti-ageing effect by activating c-Jun N-terminal kinase 1 (JNK-1) expression, leading to lifespan extension. [7] Statins were also seen to interfere with cytokine or ROS induced oxidative damage by its antioxidant effects, as well as producing cytoprotective, antifibrotic, antiapoptotic, and angiogenic actions. [18]

**Hydralazine:**

Hydralazine is a vasodilator. One of the proposed mechanisms for reducing blood pressure is to disturb calcium influx to vascular smooth muscle cells and contribute to vasodilation. Besides blood pressure lowering, hydralazine affects ageing in C. elegans by binding protein kinase A (PKA) and leading to sirt-1 and sirt-5 activation which increase mitochondrial activity and genetic stability.

Hydralazine was seen to increase C. elegans lifespan significantly under normal as well as stress conditions in reported studies. [7]

**ACE inhibitors:**

Angiotensin converting enzyme (ACE) inhibitors like captopril, lisinopril and perindopril decrease blood pressure by acting on the renin-angiotensin axis. Besides lowering BP, it is also used for reducing the mortality rate of cardiovascular disease and chronic kidney disease. The ACE inhibitor, Captopril, reduces the acn-1 activity in *Caenorhabditis elegans*, leading to life extension, increased stress resistance, and a delay in age-related degenerative changes. Further analysis indicated that the lifespan effects of Captopril act by many different pathways such as insulin/IGF-1 pathway, caloric restriction, NAD, heat shock, and mitochondria insufficiency pathways. [19]

**Rosiglitazone:**

Rosiglitazone is one of the thiazolidinediones (TZD) which stimulate peroxisome proliferator-activated receptor gamma (PPAR-gamma). PPAR-gamma stimulates insulin response genes and causes improved insulin sensitivity and thus reduces blood sugar. Besides improving insulin sensitivity, rosiglitazone has an effect of anti-ageing in mice by reducing the expression of inflammatory genes and increasing mitochondrial activity and genetic stability. All these mechanisms can extend lifespan. [7]

**Zidovudine:**

Zidovudine is a antiretroviral agents that acts by inhibition of nucleoside reverse transcriptase, preventing it from biding to viral DNA. Consequently, viruses cannot synthesise DNA or proliferate. [7] Besides being used for HIV treatment, zidovudine was seen to have anti-ageing effects in *C. elegans* by inhibiting mtDNA polymerase and reducing mtDNA synthesis. Reduction in mtDNA synthesis causes increase in lifespan.

**Acarbose:**

Acarbose is an alpha-glucosidase inhibitor acting in the small intestine, thus delaying glucose absorption. It has been used to prevent postprandial hyperglycemia in patients with type 2 diabetes mellitus. Acarbose was seen to have anti-ageing effects by inhibiting alpha-glucosidase as well. As a result of lowering the level of blood sugar, there is a decrease in the insulin/insulin-like growth factor (IIS) pathway, and this might be the reason for its anti-ageing activity. [7] Some studies have also shown that the action of acarbose in prolonging lifespan was related to short-chain fatty acids (SCFAs) in the ageing-related nutrient signal pathways. SCFAs are the main products of starch fermentation by intestinal bacteria, and are beneficial for health. Acarbose changes the intestinal flora by increasing intestinal sugar and its fermentation products, increasing the production of SCFAs, ultimately leading to a prolonged lifespan. [15]

**NAD+ Supplements:**

NAD+ is a coenzyme that mediates most of the redox reactions in a cell. The availability of NAD+

usually decreases in pathological stress and in geriatric populations, leading to a decrease in SIRTs activity in the cell. Increasing NAD+ using NAD+ precursors such as nicotinamide (NAM) and nicotinamide mononucleotide (NMN) can restore all SIRT activity in old or diseased animal cells and improve health and extend lifespan. NAD+ precursors or enzyme activators/inhibitors have shown therapeutic benefits in animal models in a wide range of age related diseases such as fatty liver, kidney injury, muscular dystrophy, cardiomyopathy, and heart failure in a SIRT-dependent manner. [6]

**SGLT 2 inhibitors:**

Sodium–glucose co-transporter 2 (SGLT2) inhibitors are used to treat type II diabetes and lower adverse cardiovascular events. In mice, renal SIRT1 is down-regulated by SGLT2, and SGLT2 blockage restores SIRT1 expression. Also, canagliflozin up-regulates SIRT1 via the AMPK pathway, improving mitochondrial biogenesis and oxidative phosphorylation. Thus, SGLT2 inhibitors exert their anti-diabetic and anti-ageing benefits partially through the activation of SIRT1. SGLT2i also reduces blood sugar and therefore insulin levels and IGF1 in type 2 diabetes mellitus, thus increasing lifespan. [6]

**Lithium and Telomere Length Regulation**:

Lithium is a nutrient-essential trace element found mainly in vegetables and drinking water. Lithium is mainly used for the prevention and treatment of bipolar disorder in practice. However, the toxicity of lithium is well known. Lithium can cause renal impairment, hypothyroidism, hyperparathyroidism, and weight gain. However, in the long term use of lithium in patients with bipolar disorder, studies found that lithium therapy prevented telomere shortening compared to the control group. Telomere shortening is an important factor in the ageing process, so lithium might have a natural anti-ageing effect. This idea was confirmed by animal studies, proving that low-dose lithium intake actually prolonged lifespan in humans. [15]

**NSAIDs and the Ageing-Related Energy Metabolism:**

Aspirin is a NSAID, a prototype cyclooxygenase inhibitor with various beneficial effects on human health. It prevents many age-related diseases and delays ageing. Aspirin prolonged the lifespan of C. elegans, Drosophila, and mice in some studies by reducing chronic inflammation via the ROS pathway. Due to the wide ranging use of NSAIDs and their well-known side effects on the gastrointestinal, renal, and cardiovascular systems, we need more ageing related clinical trials to explore the strategies that balance their anti-ageing effects and side effects. [15]

**Hyperbaric Oxygen Therapy (HBOT):**

Hyperbaric Oxygen Therapy (HBOT) achieves physiologic effects by increasing oxygen tension (PO2). Clinical and experimental studies have revealed an age-related decline in the microcirculation of the neurovascular unit, which contributes to neurovascular dysfunction and cognitive decline in ageing as well as in age-related neurodegenerative diseases. Since its first

documented use in 1662, hyperbaric oxygen therapy (HBOT) has been used to treat many different medical conditions. This noninvasive therapy is delivered by a procedure in which 100% pure oxygen is administered at higher than atmospheric pressure. HBOT has been widely researched in cerebrovascular injury such as stroke and has resulted in improved recovery time and reduction in disability rate. The beneficial effects of HBOT is via improved microcirculation by increasing tissue oxygen partial pressure (pO2), decreasing intracranial pressure, promoting tissue healing, improving metabolism, reducing apoptosis, alleviating oxidative stress, increasing mitochondrial function and promoting cell differentiation and regeneration. Although HBOT is relatively safe, it does carry some risks, mainly due to the increased pressure and hyperoxia. Most barotrauma can be prevented by ensuring good pressure equalization techniques or tympanostomy tubes. Pulmonary barotrauma and pneumothorax are very rare. Central nervous system (CNS) exposure to high (above 2,000 mmHg) pO2 may result in oxygen toxicity induced seizures. [20]

**Fatty acids:**

The levels of EPA, DHA, and total omega-3 PUFAs are significantly decreased in peripheral blood tissues of the elderly. It is well known that Omega-3 PUFAs can modulate inflammation, as well as reduce hyperlipidemia, platelet aggregation, as well as high blood pressure. Different mechanisms contribute to these effects, including stabilizing cell membrane function and composition, eicosanoid production, and gene expression. Omega-3 polyunsaturated fatty acids (PUFAs) might be an alternative therapeutic agent for sarcopenia in the elderly due to their anti-inflammatory properties, which target the age-related chronic low-grade inflammation which is assumed to cause the development of sarcopenia. In addition, omega-3 PUFAs also activates the mTOR signaling and reduces insulin resistance. [21]

**Carotenoids:**

These are phyto-pigments that give many fruits and vegetables their colour. Their antioxidant properties are known to delay brain ageing. Carotenoid-rich foods include spinach, kale, corn, bell peppers, tomatoes, watermelon, broccoli, and carrots. Carotenoids are specially used in the retina and in the brain, both structurally, and as antioxidants, via inhibiting ROS accumulation. The brain is very vulnerable to oxidative stress because of its high lipid concentrations and high energy requirements. [22]

**Vitamin E:**

Multiple studies, including RCTs, have shown that increased concentrations of Vitamin E in plasma are associated with better cognitive performance in healthy as well as ageing populations, and even in patients with Alzheimer disease. Vitamin E's efficacy is through its antioxidant properties and its ability to aid in the transporting of fatty acids. A recent RCT demonstrated that supplementation of Vitamin E, along with omega 3 fatty acids and carotenoids, improves performance in cognitive tests and working memory. Excellent dietary sources of Vitamin E include nuts, seeds, and vegetable oils

green leafy vegetables and fortified cereals. [22]

**Choline:**

Choline, an essential B-vitamin-like nutrient, plays at least two critical functions for cognitive and brain health: it is a necessary precursor for phosphatidyl-choline, the lipid making up the cell membranes and it is also required for the synthesis and release of acetylcholine, a critical brain and neuromuscular neurotransmitter. Choline benefits both cognitive function and memory. Food sources of choline include animal-based proteins such as meat, poultry, fish, and eggs, while cruciferous vegetables and certain beans are also rich in choline. [22]

**Methylene blue (MB):**

MB is a fully man-made medicine, with a wide range of clinical applications. It was already well known in surgical staining, malaria, and met-hemoglobinemia, but now, the anti-oxidative properties of MB has brought new attention to this drug in the management of ageing. Mitochondrial dysfunction leads to oxidative stress and has been observed in ageing and affects many different tissues, including the brain and skin. MB can bypass complex activities in the mitochondria and diminish oxidative stress. All these properties make MB a promising drug candidate for brain disease treatment. [23]

**Δ9-tetrahydrocannabinol:**

More than 120 phyto-cannabinoids have been identified in Cannabis. Of these, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two main cannabinoids that can lead to a temporary increase in mTOR activity and mobilization of energy resources, thus triggering the formation of new synapses. This phase is followed by reduced energy expenditure and reduced mTOR signaling in the adipose tissue, probably due to the depletion of resources in the first phase. Through this mechanism, Δ9-THC treatment combines the pro-cognitive effect of mTOR activation with the anti-ageing effect of mTOR activity blockade. Study data now suggest that a long-term low-dose Δ9-THC treatment could be a particularly effective treatment strategy against brain ageing. [24]

**Geniposidic 4-isoamyl ester (GENI):**

Iridoid glycosides are terpene-derived compounds found in plants. Iridoids have been regarded as defense chemicals against herbivorous animals and many pathogens; since they are generally bitter to taste, they are avoided by animals and insects. GENI is a new synthetic iridoid derivative that exerts anti-ageing activity through anti-oxidation and by inducing autophagy of damaged cells. In yeasts, studies show that it can prolong lifespan. Geniposidic acid is readily available from a wide range of sources, and at a low cost. Therefore, many target compounds can be easily synthesized for subsequent research for the treatment of ageing and neurodegenerative diseases. [25]

**Immunomodulation:**

Multiple groups have undertaken proteomic analysis of plasma across the life span, and several

candidate chronokines that impact the brain neurogenic functions have been discovered. The detrimental chronokines β2 microglobulin (B2M) and eotaxin can increase in ageing plasma, and their overexpression in young animals can lead to cognitive dysfunction. Antibody-mediated destruction of eotaxin can reverse their detrimental effects on neurons. Beneficial chronokines present in the young plasma of young animals have also been isolated, such as tissue inhibitor of metalloproteinases 2 (TIMP2), colony-stimulating factor 2 (CSF2), growth differentiation factor 11 (GDF11), and osteocalcin (OCN). On injection into old animals there was enhancement in their cognitive function. The identification of individual chronokines is a critical step in understanding the molecular basis of plasma-mediated biology and can provide strong rationale for therapeutic strategies. [26] The mechanisms through which eotaxin and other peripheral immune molecules contribute to disease process are still to be determined, but the identification of an association between chronokines and neurodegeneration can potentially be translated into immunomodulating therapies able to delay the onset of Alzheimer's disease in the future. [27]

**THE ETHICS OF ANTI-AGEING THERAPY**

In a just and equitable world, every person in every country, no matter their economic or educational status, should have the opportunity to live a long and healthy life. If ageing is a disease, it must be treated. But, if ageing itself a disease, there are two entities here: healthy ageing and ageing with diseases. Disease entities are treated separately and not considered a part of ageing. If we are to manage ageing so that disease entities are a preventable part of healthy ageing, then we can achieve a society where age is just a number, and health is the criteria of a well lived elderly life. Many of the therapies discussed above are related to keeping us healthy as we age biologically. Since the 1980s, the basic theme of gerontological research is a healthy, active and productive ageing. Unfortunately, today, for most world nations, population ageing is emerging as a problem of political governance, as countries the world over deal with the administrative and healthcare problems of their increasing ageing populations, without considering their health. In India, the passing of the Maintenance and Welfare of Parents and Senior Citizens Bill of 2007 (which became a law in 2009) stipulates that the family, rather than the elderly individual, the state, or the community, is the site of elder care. This law has arisen due social anxieties that with shrinking families, family-based care is declining, and what was once a moral obligation now must be implemented by law. In China, the government is proactive in encouraging daily exercise regimes and other activities to promote healthy aging. The Chinese government looks upon this as a means to reduce healthcare costs and to create a more stable social order, where, the healthy, productive elderly will not only be independent, but also contribute to society. The Chinese have also passed an "Elderly Rights Law" requiring grown children to visit their parents, and ensure their parents' financial and "spiritual" needs are met, or potentially face fines or jail. With the advent of ageing pharmacotherapy, legislation needs to be updated worldwide. As with all health promoting therapies, there must be

equity of distribution so that the rich don't hold all the cards. Whether legislation will help in this regard, only time can tell. [28]

## 2. CONCLUSION

How long can we live? How long would we like to live?

According to classic gerontology, non-repaired molecular damage causes ageing. But there are now ways to manage molecular damage and slow down or limit ageing pharmacologically. Understanding why some senescent cells are immune to ageing and others are not, could shed light on age-related senescent cell pathology, and determine whether the senescence prevention is practical in humans and how to approach their treatment. We already have some pharmacological agents which are or may be used (off label as of now) to promote healthy ageing, and also delay ageing pathology. [10] [29] As stated by Mikhail V Blagosklonny in his 2009 article, anti-ageing drugs are now a "speeding car without brakes." The train has already left the station. Let us work on this as ethically and as equitably as possible.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

No conflicts of interest to declare

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