Protective Measures to Enhance Human Longevity and Aging: A Review of Strategies to Minimize Cellular Damage

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Abstract: Aging is a universal process in all life forms. The most current and widely accepted definition of human aging is a progressive loss of function and energy production that is accompanied by decreased fertility and increased mortality with advancing age. The most obvious and commonly recognized consequence of aging and energy decline is a decrease in skeletal muscle function, which affects every aspect of human life from the ability to walk and run, to chew, and swallow and digest food. Some crucial factors responsible for aging and longevity include genetics, environment, and nutrition, serious disease disorders such as cancer and cardio-vascular diseases, sarcoma and cell senescence. Oxidative damage caused due to the accumulation of molecular waste-by-products of the body's metabolic processes, which our bodies are unable to break down or excrete, is chiefly responsible for aging and diseases. Regular physical activity, consumption of foods rich in phytochemicals and anti-oxidants, cessation of smoking, avoiding foods high in saturated and hydrogenated fats are some of the strategies that should be taken into account to delay aging and prolong longevity.

Keywords: Caloric restriction, cellular damage, bone mass, Mediterranean diet, mitochondria, telomere length.

1. INTRODUCTION

Aging of humans is a complex process with crucial changes in gene expression of biological pathways. Immune system dysfunction has been recognized as one of the most important abnormalities induced by senescent named immunosenescence [1]. Aging refers to the physical, psychological, and social changes in an organism over time. Aging has also been described as a lifelong accumulation of various types of molecular and cellular injury throughout the body. It unavoidably affects all living organisms, comprising of the build-up of macromolecular damage, genomic instability, and loss of heterochromatin [2]. Cardiovascular diseases, cognitive disorders, and aortic stiffening are some of the essential factors of aging [3]. The human body is engineered from the mechanical point of view to last for 120 years. According to the information available, the oldest person on record is Jeanne Calment of France who lived 122 years and 164 days from 1875 to 1997 [4]. It is possible that in the future, human longevity could be lengthened through genetic engineering. Globally, human populations have experienced significant increases in the average life span and while some people are living longer, but they are experiencing more years of life with numerous chronic diseases [5].

Aging of all beings begins from a single cell at the molecular level and comprises changes related to telomere shortening, senescence of cells, and epigenetic alterations [6]. Telomeres are specialized structures at the end of chromosomes that are involved in the replication and stability of DNA molecules. A telomere is a length of DNA that is made up of a repeating sequence of six nucleotide bases. The length of telomeres is positively correlated with human longevity. It is the result of inactivity/sedentariness, which is responsible for the loss of strength, stamina, and vigor. Increasing age is the risk factor for neurodegenerative diseases such as Alzheimer's because the brain's amyloid β40 and amyloid β42 are significantly increased [7]. It is associated with a progressive decline in the immune system and an increased susceptibility to infection due to the process of body "rusting" and getting rancid caused by the damaging molecules in the bloodstream known as free radicals (FR's). Likewise, the same thing happens in the human body causing it to be burned out faster. If all cellular reactions are optimum and perfect, one can lead a disease-free life, but that is very difficult to attain.

Once FR's are formed, a chain reaction can occur. These FR's pull an electron from another molecule, which destabilizes the unit; thus, it also turns into a FR. Electrons like to be in pairs, so these FR's scavenge the body to seek out other electrons to form a pair. This chain of effects can eventually damage cells, proteins

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and DNA. [8]. Trials have shown that a single nanoparticle can rapidly catalyze the offsetting of thousands of damaging reactive oxygen species molecules that are overexpressed by the body's cells in response to an injury and turn the molecules into oxygen [9]. The objective of this compendium is to describe in simple terms the aging process, cellular theories of aging and factors responsible for aging or human life span and preventive measures to delay aging-associated with improved health.

2. CELLULAR DAMAGE

Cellular damage in humans refers to an actual loss of cells; the damage occurs when cells that die and undergo senescence are not automatically replaced. Like all organisms, cells produce waste as they metabolize energy. Cellular senescence is the fundamental device of organisms aging and is closely interrelated with age-related diseases [10]. Senescence is the broad expression of human body weakening induced by various environmental factors [11]. One of the waste products of this process is a FR, an ordinary oxygen molecule with an extra electron, which is an essential factor for aging. It seeks an ordinary oxygen molecule with an extra electron, which looks to rectify by traversing about to bond with other molecules. A life-time of this can damage cells leading to cancer, arthritis, wrinkles, and a host of other diseases, thus reducing longevity.

3. THEORIES OF CELLULAR DAMAGE ASSOCIATED WITH HEALTHY LIFE

There are two chief theories of cellular damage. The first is the cellular programmed theory developed by Dr. Heyflick, which holds that human cells are programmed with biological clocks that predetermine how many times they can replicate before becoming non-functional. According to this theory, cells can only replicate 40 to 60 times before they cannot replicate themselves further [12]. Senescent cells accumulate in our bodies, making us look old by causing wrinkles, failing eyesight, and chronic inflammation. Humans age not because our cells die, but they stop dividing and start to malfunction. This cellular clock theory of aging focuses on the lifespan of cells. Since many human cells do not continue to reproduce forever, this theory proposes that aging is the result of cells striking their automated productive limit and parts of cells simply wear out [13].

The second major theory is the programmed oxidative stress theory, which holds that the human body is a cellular battlefield where cells eventually breakdown due to the attack of the caustic or highly reactive molecules called FR's that cause oxidative stress. These molecules damage our cells and tissues, making them age. In this scenario, a process called oxidation is the chief villain, which can damage vital molecules in our cells, including DNA and proteins. In the body, uncontrolled oxidation is typically caused by FR's. With cellular aging, proteostasis gradually flops, and decreased amounts and functionalities of the remaining proteins ensue [14].

Mitochondrial DNA (mtDNA) plays a vital role in aging because it signifies the primary site for the generation of cellular oxidative stress and acts as an important role in mediating programmed cell death (apoptosis) [15]. The accumulation of damage to mtDNA is, therefore strongly recognized as an important contributor to human aging. Several authors including [16], have pioneered the use of mtDNA damage as a highly sensitive biomarker of ultra-violet ray exposure and oxidative stress in human skin, thus aging- dependent mtDNA mutations can be enhanced by exposure to sunlight [16].

4. De AUBREY de GREY'S ORIGINAL THEORY OF AGING AND LIVING LONGER

Aging is described as a lifelong accumulation of various types of molecular and cellular damage throughout the body. Preventative geriatrics means to periodically repair this damage before it gets to the level of abundance that is pathogenic. Keeping the killer diseases at bay would prevent people from getting sick of old age. With stem cell therapy, a big part of it is designed to reverse one type of damage, namely the loss of dying cells not automatically replaced. These cells, one day, may be used to find ways to repair disease-damaged brains and hearts [17].

Molecular waste-by-products of the body's metabolic processes, which the human body is unable to break down or excrete, are responsible for aging and diseases. Dr. Grey and his American colleagues focus on identifying enzymes in other species that can breakdown these by-products or garbage and clean out the cells. The aim is to devise genetic therapies to give this capability to humans. Nevertheless, while knowing that aging is inevitable and we cannot expect its removal, extending healthy life span is a goal worth serious consideration. [10]. Factors such as regular physical activity, consuming a Mediterranean diet and a

variety of fruits and vegetables, eating smaller portions of food, and keeping the mind engaged could slow the aging process and increase longevity.

5. FACTORS AFFECTING AGING, LONGEVITY AND PREVENTIVE MEASURES

5.1. Bone and Skeletal Mass Decline

The aging process and its effect on the human body's ability to perform numerous functions and reduction in skeletal muscle function are described in detail [18]. The decline in the size of the skeletal muscle mass and its role with aging was described three decades ago [19]. Studies have revealed that the administration of desferrioxamine caused significant growth in bone mass via boosted angiogenesis and increased type H vessels in ovariectomized mice. Thus these data represent a novel finding that H vessels are an early marker of bone loss and represent a potential target for improving bone quality via the induction of type H vessels [20].

Since dehydroepiandrosterone (DHEA) possesses a pleiotropic effect in human aging, it may be useful in treating bone diseases through its inhibition of skeletal catabolic IL-6 and stimulation of anabolic insulin-like growth factor-1 [IGF-I] mediated devices [21]. Anti-oxidants, - chiefly berry anthocyanin, could be an active dietary agent in avoiding age-associated bone deterioration by obstructing the formation of progressive oxidation products and reactive oxygen species [22]. Predictably improved longevity is undoubtedly associated with a higher incidence of osteoporosis and difficulties associated with it. Flavonoids and statins in foods have been shown to support bone formation [23].

Levels of tumor necrosis receptor-associated factor 3 [TRAF 3] protein declines in bone and bone marrow during aging in mice and humans [24]. The development of drugs to inhibit TRAF 3 degradation in immune and bone cells could be an innovative therapeutic approach to reduce bone loss and the prevalence of several common diseases related to aging.

5.2. Caloric Restriction

By maintaining an adequate intake of essential nutrients, caloric restriction has been found to result in healthy aging in non-human primates [25]. Studies have shown that reducing the caloric restriction of 30-50% below the ad libitum level was found to increase the life span in a wide variety of species [26]. It remains the only non-genetic intervention that has been continually and dependably shown to prolong life span in a wide range of species [27]. While caloric restriction might delay biologic aging in humans, it is not clear if it would happen at the cost of significant bone loss [28]. Therefore prolonged caloric restriction may contribute to fracture risk and bone loss. However, reducing the caloric intake and glucose in the diet can result in an improved health-span and reduced cancer rate [29]. The longevity concept is flexible and straightforward; choosing foods carefully, eating nutritious foods, and cutting caloric intake slows down the aging process.

Limited intake of essential amino acids tends to slow aging by downregulating IGF-I/AKT/mTORC1 signaling; nevertheless, such low protein intake in those over 65 was related to increased risk of mortality due to a decline in glutathione synthesis [30]. Increasing cysteine uptake through adding N-acetyl cysteine or from whole protein could lessen mortality and stave off fragility [30]. Adequate animal protein alone and chiefly in combination with physical activity, is related to preserving muscle mass and functional performance in the elderly [31]. Supplementation with bioactive functional foods, such as fish, olive (*Olea europaea*) oil, lipoic acids, fruits, and vegetables along with quality protein foods, may briefly reverse the decline in renal function and serum protein in the elderly [32,33].

It has been reported that caloric restriction, reduced protein, methionine, or tryptophan diets, and reduced insulin can extend lifespan and delay deleterious age-related physiological changes in animals. Unexpectedly, low body weight in middle-aged and aged humans is accompanied by increased mortality; thus, human longevity may require pharmaceutical intrusions [34]. Other studies indicate no evidence that caloric restriction as presently practiced in humans delays immune aging related to telomere length or T cell immunoescence indicators [35].

5.3. Drugs, Organic Molecules, and Environment

Small molecules such as rapamycin, an antibiotic found in soil bacteria and resveratrol found in nuts, grapes, and berries impact hundreds of aging genes causing slowed aging in invertebrates; the potential exists to delay aging in humans using this approach [36]. Glycoprotein with a molecular weight of 22 kDa (kilodalton), extracted from unripe fruit of Rubus chingii Hu significantly increased the expression of the anti-

aging gene klotho in mice kidney and could be exploited as a dietary nutrient to slow aging and prevent age-related diseases in humans [37].

Isothiocyanates, predominantly found in cruciferous vegetables such as broccoli and cabbage (*Brassica oleracea* var. capitata) regulate the expression and function of different cytochrome P- 450 genes, and are believed to play a role against the degenerative events of aging and chronic diseases, protect from oxidative damage, and slow the aging process [38,39]. Sulforaphane, also found in cruciferous vegetables, is a promising therapeutic avenue for children with Hutchinson-Gilford progeria syndrome - a childhood premature aging disorder [40]. Further, it has beneficial health effects in longevity, and as an anti-aging drug, it may counter with anti-senescence activity through glucose and glycolytic response as it may protect against inflammation, inhibiting cytokine production [41,42,43]. Kimchi (fermented cabbage) - a traditional Korean food has been shown to be health-promoting, with antioxidant and anti-aging properties [44].

In the past, significant increases in human lifespan have been found due to the improvement in living environments reducing infection as a cause of death through better hygiene, nutrition, population control, public health, and from the burning of fossil fuels [45]. Genetic discrepancy explains only 20-25% of the variability to regulate aging, while factors such as environment, epigenetics, and life-style additionally contribute to the aging process [46].

5.4. Free Radicals and Anti-Oxidants

Free radicals are probably one of the most crucial factors affecting aging and longevity. Toxic chemicals, smoking, the sun's rays, strenuous exercise, and environmental pollution are some of the factors resulting in the formation of FR's. Hundreds of thousand-s of FR's are enemy invaders to damage or destroy the body cells or changing them into unhealthy ones. In response to the attack by FR's, antioxidants in a combating mission are charge in to neutralize this enemy and keep the cells that make up the human body in healthy shape [47]. The villain is oxygen, which becomes harmful when it's converted into a FR. The FR replaces that missing electron and can get it by taking a bit out of another molecule [47]. These FR's can permanently alter the DNA and cause mutations of cells, which may lead to cancer. The FR's are random bits of matter, which will attack any part of the body, any organ system and any cell hastening the aging process.

The human body natively produces antioxidant enzymes called glutathione peroxidase, superoxide dismutase, and catalase [48]. However, these are quenched by the FR's so there aren't enough of these to go around to neutralize this powerful enemy. The most important step is to supply the body with the major antioxidants - vitamins A, E and C, beta-carotene, and minerals such as selenium (Se) and iron. Selenium enhances the activity of the enzyme glutathione peroxidase. Likewise, the antioxidant vitamin E increases the activity of superoxide dismutase by scavenging FR's [47]. The metal iron is vital for catalase since the non-protein part of catalase is a derivative of heme and includes the metal iron. Thus, the more antioxidants the body has in the system, the better able it is to halt FR's damage and thus slow or stop the progression of diseases and the ageing process itself. Antioxidants are the key to turning the immune system around; because they fight FR's that are locked into destroying them. Boosting the intake of vitamins and minerals, herbs, and other foods high in antioxidants will reduce damage caused by FR's [47].

5.5. Fruits, Vegetables, and Phytochemicals

Consumption of a Mediterranean diet consisting of olive oil, fruits, and vegetables has been associated with longer life and possible protection against the growth of endothelial dysfunction through increasing endothelial progenitors and circulating progenitor cells [49]. This diet is also beneficial in preventing low-grade inflammation and cardiovascular disease, which are age-related diseases, and have a positive effect on aging [50,51]. Diets rich in fruits and vegetables are associated with reduced risk of chronic diseases, which are prevalent in the aging population. Results of long-term studies indicate that adherence to this diet, regular physical activity and non-smoking are strongly associated with a reduced risk of all-cause mortality in healthy subjects and higher levels of cognitive function in the elderly and may be the chief neuroprotective strategy [52,53]. An earlier study reported that a traditional Dutch diet, which includes a high intake of vegetables, fruits, non-alcoholic drinks, dairy products and potatoes, rather than a Mediterranean diet also appeared beneficial for longevity and reasonable for older Dutch women [54]. The primary difference is that the Mediterranean diet also contains fish and oils.

Numerous fruits and vegetables contain phytochemicals rich in triterpenoid found in fruit peel and particularly in fruit cuticular waxes, and are

biologically active compounds. Triterpenoid decreases the risk of chronic diseases [55]. Lycopene found in large quantities in tomatoes (*Solanum lycopersicum*); ascorbic acid, phenolics and tannins in star fruit (*Averrhoa carambola*) all have intense anti-oxidative activity, which could remove FR's of oxygen to delay the aging of cells or cellular aging and disease prevention in humans [56,57]. Consumption of legumes, such as, pulses, peas (*Pisum sativum*), beans (*Phaseolus vulgaris*) and lentils (*Lens culinaris*) have been found to be associated with reduced risk of several chronic diseases and in promoting optimal health, which should lead to healthy aging [58,59].

It has been suggested that phytochemical supplementation provides beneficial effects for normal aging and also delays the onset of age-related neurodegenerative diseases [60]. The anti-inflammatory mechanism of another important anti-oxidant, quercetin conjugates in macrophages, offers a possible strategy for the effective utilization of natural polyphenols in the daily diet to prevent age-related chronic diseases [61]. Recent studies show that antioxidant phenolic compounds from pear (*Pyrus ussuriensis Maxim*) could be used therapeutically in the prevention of human diseases [62]. An antioxidant molecule oligonol, with polyphenolic properties, found in lychee (*Litchi chinensis*) fruit has been found to be anti-inflammatory with anti-cancer properties and considered an anti-aging molecule [63]. Gallotanin, a type of polyphenol found in grapes (*Vitis vinifera*), berries, in aronias (*Rosaceae family*) and in acorn (*Quercus macrocarpa*) nuts have been found to protect the skin against UVB rays and acts as an antiaging agent [64]. Studies on parboiled germinated brown rice (*Oryza sativa*) extracts show that it prevents carbon tetrachloride-prompted liver oxidative stress and injury through enhancement of bioactives, such as phenolic acids - oryzanol and γ-tocotrienol [65].

The polysaccharide TLH-3 extracted from edible fungi has been found to possess antioxidant and anti-aging activities and could be exploited as a potent dietary supplement to attenuate aging and prevent age-related diseases in humans [66]. Salicylates in plant extracts activate adenosine monophosphate-activated kinase and are now thought to be a promising target to slow down aging and avert age-related diseases in humans [67].

The higher life expectancy of people in Latin American and Caribbean countries is considered to be due to their consumption of fruits and vegetables in addition to engaging in physical activity [68]. In Western European nations, healthy aging is related to adequate nutrition along with physical activity, which are crucial domains to healthy aging [69,70]. It has been recommended to increase the consumption of vegetables, particularly cruciferous vegetables and fruits to stimulate cardiovascular health and longevity [71]. In general, people who eat a healthy, mostly plant-based diet may be less likely to develop heart disease and to die from it than those who consume a large quantity of meat and refined carbohydrates.

5.6. Mitochondria, DNA, and Genetics

One of the essential factors in human aging is the accumulation of DNA damage during one's lifetime [72]. This theory of aging proposes that the build-up of damage to mitochondrial function and DNA mutation leads to the aging of humans. Mitochondria play a dynamic role in functional responses of synaptic activity and thus, the deterioration of mitochondrial function can lead to severe neuronal energy shortage and neurodegeneration in the aging brain [73]. Base excision repair is an essential DNA repair pathway involved in the maintenance of genome stability and thus in the prevention of diseases such as premature aging [74]. Mitochondrial dysfunction has arisen as one of the crucial trademarks of the aging process and is related to the growth of several age-associated diseases [75].

Automated cell death is a basic cellular characteristic. According to the reversed Warburg theory formulated by Demetrius, pathological aging is brought by mitochondrial respiration. Hence stimulation of mitochondrial metabolism is responsible for pathological aging [76]. It has been established that there is almost no fixed program for aging, which is caused instead by the lifetime damage build-up [77]. Mitochondria-targeted anti-oxidants may represent a novel promising therapeutic strategy for decreasing disorders, such as aortic stiffening associated with aging [3]. Neurons acquire an unusually high burden of wear and tear, this is likely why age is considered to be the most influential risk factor for the development of Alzheimer's disease [78]. The highest mean density of Von Ecnonomo Neurons (VON) in super-agers showed that it was an indicator of extended longevity.

Genetic background is a significant aspect of longevity in addition to well-recognized factors including life-style, environment, nutrition, physical activity, smoking and alcohol. Obesity is negatively associated with health and longevity [79]. Smoking

cigarettes encourages premature aging and mitochondrial dysfunction leading to the secretion of high energy mitochondrial fuels; hence it brings catabolism in the local microenvironment [80]. Smoking induces the "reverse Warburg effect", thereby resulting in oxidative mitochondrial metabolism in epithelial cancer cells. Factors such as genetics, lifestyle conditions, including nutrition, socio-economic parameters, as well as the number and recurrence of pathogens accrue during aging in the elderly. Consequently such individuals may have seen more chronic stimulators and have experienced more reactivation episodes ultimately leading to shrinkage of their overall immune health [81]. Genetic and chemical perturbations can extend life and health span as revealed in model organisms [82]. Animal model studies have shown that it is possible to prolong lifespan and delay some aspects of the aging process, either by modulating a genetic pathway or supplementing chemicals. Similar results could be experienced in humans [83].

Genetic pathways affect longevity as well as metabolism and growth. The mechanical target of rapamycin, sirtuins, adenosine monophosphate-activated protein kinase, growth hormone/insulin-like growth factor and mitochondrial stress-signaling pathways impact aging and life span in abundant species and there are likely implications for delaying aging in humans [84]. Faultless human stem cell genetic consistency would prevent aging and cancer; however that would be hard to achieve as aging is wide-spread and cancer is common [85].

5.7. Nutrients, Minerals, Hormones, and Food

Although carbohydrates are essential nutrients, abnormal regulation of their metabolism is associated with diabetes, cardiovascular disease, and stroke; thus, diets enriched in glucose are related to accelerated aging in numerous model organisms, such as yeast and *Caenorhabditis elegans* (a species of round worm that is a soil-dwelling nematode)[86]. Human longevity with a higher number of elderly people in the coastal and southern regions of China has been attributed to higher levels of Se and omega-3 fatty acids in sea fish [87]. Dietary patterns in individuals over 70 years of age have not shown an association with serious human diseases. However, an association has been observed between the red meat and protein alternatives with cancer development and death [88]. Proteomics and a powerful model will likely be required to determine the underlying biological processes that affect natural variation in age-related diseases and longevity [89].

The age-related reduction of growth hormone secretion together with benefits of growth hormone treatment in individuals with adult congenital or adult growth hormone deficiency supports its role as an anti-aging agent [90]. Reduction in the secretion of growth hormone is associated with a decrease in muscle and bone mass and loss of vitality [91]. This indicates that growth hormone treatment in adults may become an effective tool for use in preventive medicine. Nutrients such as γ-tocotrienol, a vitamin E isomer may prevent cellular aging of human diploid fibroblasts by modulating gene expression [92]. Ginkgo (*Ginkgo biloba*) seeds protein has also been found to have anti-oxidation, antibacterial and anti-aging properties and has high value for nutrition [93]. Ginsenosides are the main anti-aging compounds of ginseng, which defend the nervous system from aging by stimulating human intelligence, preventing the release of lactate dehydrogenase (LDH) and methylenedioxy-amphetamine (MDA) and reducing intracellular calcium [11].

Studies have shown that there is a relationship between the mineral Se, anti-carcinogenic potency, and the regulation of cell growth, and thus it will affect human longevity [94]. It has been found that the addition of Se significantly improved the DNA repair in the keratinocytes, which have an augmented susceptibility to oxidative DNA in the elderly. This study suggests that Se strengthens DNA repair activities and represents a new strategy to combat aging and skin photoaging [95]. Diets rich in fruits, vegetables, nuts, legumes, low-fat dairy and lean meats are related to healthy aging and inversely associated with mortality [96,97,98]. These diets considered healthy are also associated with higher skeletal muscle mass which plays a vital role in people above 60 in healthy aging [99].

5.8. Oxygen and Oxidative Stress

Oxygen is essential to human existence and yet this highly reactive unutilized gas is converted into FR's, which are killing us. On the other hand, oxygen is very important as a source of fuel utilized by mitochondria to produce energy and release nutrients for the body. The FR's are highly reactive because they are missing electrons and constantly hook up to capture electrons from other molecules. Thus, they become highly unstable and dangerous. When the cells get overwhelmed with oxidation, it results in oxidative stress, which is linked to inflammation and chronic diseases. [100]. Oxygen's essentiality and toxicity,

when converted into FR's, is known as the "oxygen paradox" to describe this strange dual nature.

Oxidation can result in DNA damage, mutations, improper cell division, and could result in pre-cancerous reactions [100]. FR's are produced through metabolism and are delivered through the blood-stream. They are widespread, coming to the body from the sun's rays, soils, foods, environmental pollution, emotional stress, normal metabolic processes, aging, smoking, and traumatic events such as wounds and burns. They attack cells, destroying many and even altering DNA, and making it impossible for the cell to reproduce itself. Thus the cells are weakened and are vulnerable to cancer invasions. These FR's can tear apart important biological molecules and cause damage through the electrical decoupling at the level of cellular DNA. Their reactive nature alters the DNA, and the cell is unable to produce the right protein or produces too much protein thus converting them to cancerous cells or producing cancerous changes [100]. With incorrect proteins, the heart and cardiac muscles are weak. Thus the FR's can increase the risk of cardiovascular disease, heart attack, atherosclerosis, and chronic obstructive pulmonary disease.

However, antioxidants are able to mitigate this damage by pairing up with a stabilizing proton, turning these potentially harmful molecules into something benign. These include some vitamins, carotenes, glutathione and the antioxidant enzymes - catalase, superoxide dismutase, and glutathione peroxidase. The enzymes have the potential to neutralize many FR's with greater speed and precision than vitamins and carotenes. Foods, e.g., cruciferous vegetables, such as broccoli (*Brassica oleracea* var. italica), cauliflower (*Brassica oleracea* var. botrytis), cabbage and berries (*Ericaceae* family) may contain compounds that could activate the body to increase its own endogenous antioxidants and enzymes [100]. Compounds in cruciferous vegetables can defend against hungry insects. All body disorders resulting from the oxidative damage are bound to reduce human longevity to some extent.

5.9. Pathologies and Diseases of Organs

Aging is the principal risk factor for several common and chronic diseases that support physiological aging [101, 102]. Neurodegeneration and cancer are associated with aging, which is influenced by environmental and genetic aspects. FOXO proteins, important transcription factors, are chief reasons in aging and longevity [103, 104]. Normal aging of lungs is manifest by molecular changes that occur during growth, maturation, and late-life decline. It correlates strongly with the growth and incidence of respiratory diseases and is strongly linked with chronic obstructive pulmonary disease [105]. Lung failure due to aging can be traced to the loss of lung stem cell regenerative capacity within the distinctive stem cell niches found within each compartment of the lung. Aging serves as a self-regulating factor for long-lasting diseases, such as cancer, pulmonary, neurodegenerative, and cardiovascular diseases. Autophagy destroys and removes long-lived or impaired cellular organelles and proteins. This ability declines with aging that can be introduced using anti-oxidants, e.g., rapamycin, resveratrol, nicotinamide derivatives which prolong the lifespan [106].

Studies have shown that the number of teeth in aging humans can affect longevity and life expectancy. This is attributed to the fact that loss of teeth impairs the quality of life measures including the eating of most foods and full mastication function allowing their release of nutrients [107]. Similar studies have been reported where reduced chewing ability due to the loss of teeth in the elderly accompanies the aging process [108]. Intestinal transcription factor homolog Fork Head (FKH) protein has been found to extend lifespan. Such a pro-longevity effect has been attributed to the gut, and there is increased expression of nutrient transporters and improvement of barrier function by FKH activity [109]. The degree of aging differs between people of the same age, meaning that the biological age of an individual may be different from chronological age. Aging represents a very potent risk factor for diseases and disability related to age-associated cellular processes, oxidative stress and the regulation of zinc homeostasis [110].

Aortic stenosis and coronary artery disease share similar risk issues related to the aging of the human population. For example, patients undergoing processes of combined aortic valve replacement and coronary artery bypass grafting have more widespread coronary artery disease less often receive complete revascularisation, are at higher risk of early organ failure, and present reduced rate of freedom from cardiac-related deaths than younger subjects [111]. Aging can have detrimental effects on the progression of neurological disorders and brain diseases and endogenous stem cells. Stem cell therapy offers the potential to mitigate the neurological symptoms of such diseases [112]. Recently heterochronic parabiosis

relating surgical attachment of old and young animals sharing common vasculature has shown that systemic environment has a profound influence on stem cell function and may re-establish the regeneration process and even reverse human tissue aging [113].

Treating metabolic syndrome would be beneficial in avoiding disability and supporting normal aging. In this regard, fermented milk with *Lactobacillus plantarum* (Lactobacillaceae family) has shown favorable results in relation to cardiovascular risk issues in postmenopausal women with metabolic syndrome [114].

5.10. Physical Activity, Telomere Length, Frailty, and Sarcoma

Leukocyte telomere length is positively associated with age-related diseases. It has been found to correlate inversely with smoking, age and a variety of phenotypical behaviors [115]. Exhausting exercises and physical load, prolong life expectancy, increase survival chronological age since they have a positive effect on telomere length, which is an important biomarker for aging-associated with parental lifespan [116]. Shortening of telomeres, in part, is a changeable factor, and evidence shows that adherence to the Mediterranean diet is related to longer telomeres [117]. Moderate and intensive training exercise life-style diminishes the effect of aging on the immune system and telomere length. Both of these training groups had longer telomere in T cells [118]. Physical inactivity and aging are related to the development of insulin resistance, whereas physical activity has been found to reduce insulin resistance. While a sedentary lifestyle could have an impact on the metabolism of human myotubes during aging and may contribute to aging-associated insulin resistance through impaired glucose transporter type 4 (GLUT4) localization [119]. Hence regular physical activity will add life to years, but not necessarily years to life.

It has been reported that entropy generation increases with physical activity suggesting that exercise should be kept to a “healthy minimum” if entropy generation is to be minimized [120]. Studies in the elderly people show that age-related maladaptive changes are more prominent in humans with a high degree of frailty [121]. Aging muscle weakening is, in part a neurodegenerative process, and hence exercise training has demonstrated neuromuscular benefits in aged humans and animals [122]. Aerobic exercise can up-regulate the expression of excision repair protein (ERCC1) and thus may reduce DNA damage accumulation to retain genomic integrity and stability thereby delaying aging and prolonging lifespan in humans [123].

Predictable and dedifferentiated chondrosarcomas mostly affect people in their 4th to 7^{th} decade of life [124]. At early stages, chondrosarcomas are still thought to be an intermediate type of tumor which seldom metastasizes. Regrettably, advanced stages show a pronounced resistance both against chemo- and radiation-therapy and often metastasize.

5.11. Senescence

Senescence is the complete exhibition of human body weakening induced by many environmental causes. Cellular senescence is the underlying cause of organism aging and is closely interconnected with age-related disease [10]. Mineral Se at a nutritional level is vital for the biosynthesis of selenoproteins. However, excess Se could prompt the formation of reactive oxygen species. Therefore understanding the biotic role of Se in senescence may assist in optimizing human health through delayed aging and age-related diseases [125].

Du-Huo-Ji_Sheng-Tang (DHJST) and its dynamic constituent L. chuanxiong are able to stimulate osteogenic activity and decrease human mesenchymal

Table 1: Aging Symptoms, Factors Affecting Aging and Preventive Measures

Symptoms of Aging	Factors Affecting Aging	Preventive Measures
Loss of function and energy production; body skin changes; deterioration of eye-sight and hearing; decreased skeletal muscle function; immune function dysfunction; processing of brain speed is slower; declining activity of autophagy; DNA damage resulting in mutations; emotional stress; trouble in bodily joints; apnea, trouble with sleeping; cognition difficulties.	Genetics; environment; serious disease disorders, e.g., cancer, cardiovascular disease; smoking; cell senescence; accumulation of waste molecular by-products, chiefly known as FR’s; inactivity; pollution from fossil fuels; sun’s rays.	Regular physical activity; cessation of smoking; avoiding saturated and hydrogenated foods; caloric restriction; consuming plant-based foods; Mediterranean diet; consuming lean meats; antioxidant intake, e.g., foods rich in flavonoids, beta carotenes, anthocyanin, polyphenols and micronutrients, such as Vitamins A, C and E; minerals-selenium, zinc; consuming omega-3 fatty acids; turmeric; ginger; legumes; cruciferous vegetables and fruits.

senescence as cells age [126]. Although cellular senescence is emerging as a key mechanism of age-related vascular endothelial cell dysfunction, evidence in healthy humans is lacking. However, results in humans indicate that increased endothelial cell senescence occurs with sedentary aging, which is absent in older exercising adults [127].

A summary of symptoms of aging, factors affecting aging and preventive and control measures for slow and gradual aging are reported in Table **1**.

5.12. Effect of Undoing Changes in Gene Activity

Recent investigations suggest that aging is largely a process of epigenetic changes, alterations that make genes more active or less so as summarized [128]. With changes, the muscles weaken, minds slow down and the body becomes more vulnerable to diseases. It is possible to slow or reverse aging, at least in mice by undoing changes in gene activity-the same kind of changes that are caused by decades of life in humans. Yamanaka factors critically regulate a signaling network composed of a number of crucial regulating pathways to maintain the pluripotency of embryonic stem cells and likely to induce pluripotent stem cells [129]. According to the study, reprogramming epigenetics should work on mice and humans and even cells from centenarians could eventually be rejuvenated [128]. Interventions that slow aging will have a greater effect on quality of life compared with disease-specific approaches [130]. Studies indicate that epigenetic shift is in part responsible for aging, and reprogramming can correct these epigenetic errors. Future studies are planned on how to reprogram to be young again without taking it too far so they become tumors [128]. As discussed earlier in this article, other factors, such as caloric restriction, rapamycin, resveratrol and parabiosis have anti-aging properties to delay epigenetic changes and protect against damage from epigenetic deterioration.

6. AGEISM IN MEDICINE

Ageism is stereotyping, prejudice and systematic discrimination against people on the basis of their age and one could debate that the health care system discriminates against older adults in several ways. These attitudes lead to the marginalization of older people and have a negative impact on their health and well-being. People age differently in dissimilar ways and at unlike rates. For older people, ageism is every day's challenge. In their 60s and 70s, people's joints may start to give physical difficulties and skin changes. Their hearing and eyesight deteriorate, they begin to lose muscle mass and the processing speed of the brain is slower. In their 80s and above, people start to develop more stiffness and their probability of falling increases and they have trouble with sleeping and awareness, the so-called geriatrics disorder [131].

7. BLUE ZONE LIVING

People living in blue zones have the highest longevity in the world. These regions include the Italian island of Sardinia, the Japanese islands of Okinawa, the Greek island of Ikaria, Costa Rica's Nicoya Peninsula, and around Loma Linda, California. For most of their lives, these world's super-agers have nourished their bodies with whole, plant-based foods, such as leafy vegetables, tubers, nuts, beans and whole grains [132]. On average, they eat meat fewer than five times monthly. To live a long healthy life, the key is to do the right things and avoid the wrong things for decades, not just a few months. Because when it comes to longevity, there's no short-term fix. People in blue zones have been eating the "right" foods because the right foods such as beans, grains and garden vegetables are also the cheapest and most accessible. People also benefited from having a circle of lifelong friends, a clear sense of purpose, an environment that nudged them into constant movement, and daily rituals that mitigated stress. Their communities are built for people, not cars. Every visit to a friend's house, the market or workplace occasioned a walk. The most important step on one's journey to a healthy 100 years might be to start living and eating like they do in the blue zones [132]. Policy-makers could play an active role in promoting the benefits of fruits and vegetables consumption for healthy aging among the rural elderly [133].

SUMMARY AND CONCLUSION

Aging is the universal constant and the single threat to the development of disease [134]. It is a process of slow well-designed functional weakening at the cellular and organismal levels. Thus, the study of premature aging is helpful in understanding the physiological development of human aging and is beneficial in the prevention of age-related diseases [135]. The relevance of lipid signaling in aging represents an unexplored area for health-promoting and life-extending interventions. Aging is a complex process with crucial changes in gene expression of natural pathways. While knowing that aging is inevitable and

we cannot presume its abolition, prolonging a healthy life span is a goal that deserves thoughtful consideration [10]. To live a healthy life requires avoiding overeating, consuming nuts and plant-based products, having a high intake of antioxidants and phytochemicals such as turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), consumption of fruits and vegetables, getting enough sleep, and avoiding chronic stress and anxiety.

A relatively recent discovery is that regulating the activity of telomeres by telomerase is a key factor of aging. It refers to the fact that the length of telomeres is positively correlated with human longevity. The chief factors affecting the telomere length are suffering less stress, regular physical activity, consumption of foods high in antioxidants and vitamins and practising meditation [136]. Aging is a direct result of three factors: people consuming too much food, getting inadequate physical activity and suffering too much stress. People should consider eating less meat and more fruits, vegetables, whole grain foods and nuts, since human beings are not born carnivorous. Aging is largely a process of epigenetic changes, alterations that increase or decrease specific gene function. Finally, while aging and longevity are beyond human control, healthy habits as suggested in this article and elsewhere [137] may position humans on a path to healthy aging.

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