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Review Article

The modification of aging process

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ABSTRACT

Aging is a gradual, continuous process of natural change that begins in early adulthood. During early middle age, many bodily functions begin to gradually decline. Aging is a multifaceted biological process that affects all organs and organ systems of the body. Dietary restriction and exercise have been found to extend human lifespan. Exercise, Dietary supplements, antioxidants, preventive intervention can delay aging process.

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1. Introduction

1.1. Definition

Aging can also be defined as a progressive functional decline, or a gradual deterioration of physiological function with age, including a decrease in fecundity. WHO defines Healthy Ageing "as the process of developing and maintaining the functional ability that enables well being in older age"[1A]

There were about 700 million persons aged 65 years or over in the world in 2019. The number of older persons is projected to double to 1.5 billion in 2050. Globally, the share of the population aged 65 years or over increased from 6 per cent in 1990 to 9 per cent in 2019. That proportion is projected to rise further to 16 per cent by 2050, so that one in six people in the world will be aged 65 years or over.[1B] Different Types of Aging: Chronological Aging Chronological Aging is the number of years a person has lived so far. However, chronological age may not match a person's biological, psychological, or social age.

Biological Aging involves the loss of cells over time. With biological aging, tissues and organs are less likely to function efficiently, the body's ability to repair itself slows down, and the immune functions decline, making the body more prone to infection. Cognitive function also becomes less effective with age.

Psychological Aging involves changes in memory, learning, intelligence, personality, and coping.

Social Aging refers to changes in a person's roles and relationships, both within their networks of relatives and friends and in formal organizations such as the workplace and houses of worship.[1]

1.2. Mechanisms of Aging

1.2.1. Programmed theory

Ageing is the result of a sequence of events encoded in the genome just as the developmental sequence is controlled by gene expression**.**(Figure 1)

1.2.2. Error theory

In many respects this theory is a derivative of the somatic mutation theory since it is based on the idea that species differences to tolerate DNA damage may explain

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Fig. 1:

the variations in life span. Orgel proposed a model for biological ageing that was based on a decrease in the fidelity of protein synthesis.

1.2.3. Free radical theory

(Figure 2) Free radicals are highly reactive atoms or molecules in which an electron pair has been separated into two electrons that exhibit independence of motion, and are capable of initiating a chain reaction with stable molecules to generate more free radicals. Free radical formation and oxidative activity have been proposed as the basis of certain pathological states such as fibrosis of arterioles and capillaries secondary to membrane damage. The free radicals are implicated in such pathologies as cancer, cardiovascular diseases, degenerative diseases of the central nervous system and the functional decline of the immune system.

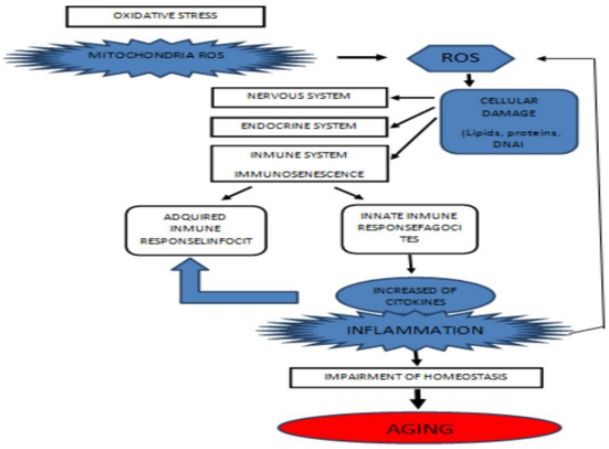

Fig. 2:

1.2.4. The Cross-Linkage Theory

Many common biological macromolecules will form covalent links between component parts of the same molecule or between molecules thereby modifying both structure and function. Cross-linkages in DNA and protein have been demonstrated. More linkage with aging is known,

1.2.5. Accumulation Theory

The accumulation of waste products within cells such as lipofuscin, a yellow green fluorescence product of lipid peroxidation involving the lysosomes. Such age pigment accumulates particularly in post-mitotic cells, such as neurones and cardiac muscle.

1.2.6. Immunological Theory

Concurrent with the decline in immune response, particularly in the T cell component is an increase in autoantibodies. It is proposed that the linkage of the genetic control for these factors on chromosome 6 in humans.

1.2.7. Neuroendocrine theory

Disregulation of neuroendocrine control through neuron loss, neurotransmitter deficiencies, stress, hypopituitarism, hypothyroidism, or disruption of feedback sensitivity.[2]

1.3. Aging process and Telomeres

The length of telomeres in the cells of older people tends to be shorter than in younger people Telomere shortening has therefore been identified as a factor that could contribute to aging It is well established that telomere length and telomerase activity are important factors in the pathogenesis of human diseases Atherosclerosis is also an aging-related systemic disease. Telomere length is a new marker of cardiovascular risk. In the vascular endothelium, shorter telomeres are found in those areas of the arterial wall that are more susceptible to atherosclerosis because of higher haemodynamic stress. Telomere shortening provides a tumor suppressor mechanism to cease the growth of transformed cells. Telomeres were significantly associated with type 2 diabetes, which could be partially attributed to the high oxidative stress in the patients with type 2 diabetes.

1.3.1. Premature Aging

Premature aging, called also accelerated aging, is a group of genetic syndromes, in which the children have premature aging. The three known premature aging syndromes of human being are Hutchinson–Gilford Progeria Syndrome (HGPS), Werner syndrome (WS), and Cockayne syndrome (CS).[3]

1.4. Consequences of Aging[4]

Common health conditions associated with ageing. Common conditions in older age include hearing loss, cataracts and refractive errors, back and neck pain and osteoarthritis, chronic obstructive pulmonary disease, diabetes, depression, and dementia.

The triad of hypertension, high lipid and type 2 diabetes in middle aged or old also called syndrome X is shown in diagram below. It is marked by abdominal obesity, elevated levels of triglycerides, low levels of HDL. Cardiovascular complications such as heart attack and stroke are not uncommon.

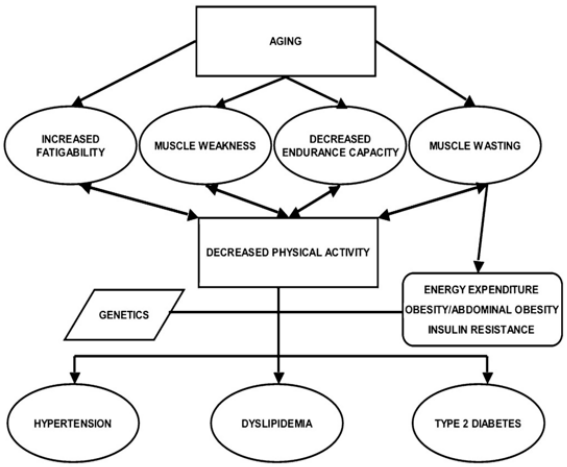

Fig. 3:

1.5. Age related changes in Pharmacodynamics and kinetics:

Ageing produces major cardiovascular changes, including reduced elasticity and compliance of the aorta and great arteries. This results in a higher systolic arterial pressure, increased impedance to left ventricular ejection, and subsequent left ventricular hypertrophy and interstitial fibrosis. Renal mass decreases with age. This reflects the reduction in nephrons. Both renal plasma flow and glomerular filtration rate decline with age. Secretion of hydrochloric acid and pepsin, which are decreased under basal conditions, Advancing age is associated with a progressive reduction in liver volume and liver blood flow. Excessive HPA (hypothalamic-pituitary adrenal activation) and hypersecretion of glucocorticoids can lead to dendritic atrophy in neurones in the hippocampus, resulting in learning and memory impairment. There is a progressive reduction in total body water and lean body mass, resulting in a relative increase in body fat.

Reduction in renal function in elderly subjects, particularly glomerular filtration rate, affects the clearance of many drugs such as water-soluble antibiotics diuretics, digoxin, water-soluble b adrenoceptor blockers, lithium , and nonsteroidal anti-inflammatory drugs. The absorption of vitamin B12, iron and calcium through active transport mechanisms is reduced. Reduced b-adrenoceptor function is observed with advancing age. Elderly patients are less sensitive to the chronotropic effect of isoprenaline. Advancing age is also associated with increased sensitivity to the central nervous system effects of benzodiazepines[5] Cimetidine is associated with more clinically important drug interactions than the other histamine-2 antagonists and this medicine can cause several adverse effects, such as bradycardia, arrhythmias, confusion, depression. Famotidine and other proton pump inhibitors that present less anticholinergic properties than ranitidine, are preferable in order to avoid these effects in elderly patients All health professionals should be aware of the changes occurring in elderly individuals, and those prescribing drugs should always take the changes occurring in drug pharmacokinetics and pharmacodynamics during aging into consideration, in order to avoid compromising the health of the elderly through inappropriate prescriptions.[6]

Pharmacotherapy mishaps among elderly patients are a major healthcare issue and a problem for all healthcare practitioners treating elderly patients. Physicians, nurses, pharmacists, nurse practitioners, physicians' assistants, and patients' families and caregivers are responsible for improving the care provided to elderly patients.

1.6. Antiaging drugs

1.6.1. Anti oxidants

These are molecules that can neutralize free radicals by accepting or donating an electron to eliminate the unpaired condition. They are natural scavengers of free radicals, known to cause cellular damage and consequent agerelated medical disorders (including wrinkling of skin). Antioxidants' antiaging benefit is due to their anti-inflammatory effect, delay or prevention of cancer, diabetes, and brain disorders

Antioxidants have greater anti-inflammatory and anticarcinogenic effect and the resultant anti-aging effect, when they are consumed in their natural food source than individual antioxidant elements. Antioxidants neutralize these damaging free radicals by quenching the reactive molecules, thereby protecting cells from endogenous and exogenous stressors and prolonging their life and vitality.

Enzymatic antioxidants include glutathione peroxidase, superoxide dismutase and catalase; non-enzymatic antioxidants include vitamin C, glutathione, vitamin E, coenzyme Q10 (ubiquinone-10), and alpha lipoic acid.[9]

1.7. Other vital Compounds

Resveratrol The effects of resveratrol in rodent studies of age associated disease have been impressive, questions have emerged regarding the degree to which its effects can be attributed to activation of sirtuins. In addition to sirtuins, resveratrol is reported to inhibit or activate more than 15 different enzymes,

The recent discovery that the mTOR inhibitor rapamycin extends mammalian lifespan has created much excitement because it represented the first demonstration of pharmacological extension of maximal lifespan in a mammalian species**.** Rapamycin was found to suppress cancers and extend life in a range of genetic early-onset cancer models, such as p53 mutant mice, Apc mutant animals, Rb mutant mice and HER-2/neu transgenic mice. Decrease in inflammation and hypertrophy Higher

Table 1: Pharmacodynamic changes in drugs with Aging

Drug class	Potential pharmacodynamics issues	Comments
Antihypertensives	Orthostatic hypotension	Additive effect at lowering blood pressure Use with caution Start with lower dose
Benzodiazepines	Increased sensitivity (eg, drowsiness, confusion)	Use with cautionAvoid other central nervous system—active drugs Use lowest tolerable dose
β –Adrenergic blockers (eg, propranolol)Anticoagulants (eg, warfarin)	β-receptors less responsive Greater sensitivity to drug action	May require greater β-blocker doses to have same effect Initiate with lower dose Follow international normalized ratio closely
Diuretics	Greater sensitivity to drug action	Monitor blood pressure and electrolytes

Table 2: Drugs causing problems inelderly[7]

Drug	Adverse Effect
Nonsteroidal anti-inflammatory drugs (eg, ibuprofen, naproxen)	Gastrointestinal bleeding, renal dysfunction
Diuretics (eg, hydrochlorothiazide, furosemide)	Hypotension, dehydration, electrolyte disturbance
Warfarin	Bleeding, many drug interactions
Angiotensin-converting enzyme inhibitors (eg, lisinopril)	Hypotension, renal dysfunction
Antidepressants (eg, morphine)	Confusion, Hypotension, Consitipation
Opiates	Confusion, disorientation, Consitipation
Prednisone	Osteoporosis, gastrointestinal problems, hyperglycemia
Benzodiazepines (eg, lorzepam)	Drowsiness, Confusion

Table 3: Disease being aggravated by use of drugs[7]

Disease State	Aggravating drug	Potential Adverse Effect
Diabetes	Corticosteroids (eg, prednisone)	Drug-induced hyperglycemia
Osteoporosis	Corticosteroids (eg, prednisone)	Increased Fracture risk
Constipation	Anticholinergics/antihistamines/narcotics	All show gastrointestinal tract motility
Parkinson	Antipsychotics	Aggravate Movement Disorder
Hypertension	Nonsteroidal anti-inflammatory drugs	Fluid retention increases blood pressure
Benign prostatic hypertrophy	Anticholinergics/ antihistamines	Urinary problems

Table 4: Antioxidants in food

Antioxidants	Major Dietry Sources
β-Carotene	Carrots, yellow papaya Spinach
Vitamin A (Retnoids)	Garlic, ginkgo boloba, tomatoes
Vitamin C(Ascorbic Acid)	Citrus fruit, spinach cabbage, garlic
Vitamin E (Tocopherols)	Vegetable oils, legumes
Lycopene	Red tomatoes
Lutein and zeaxanthin	Egg yolk
Polyphenols	Apple
Querectin (a flavonoids)	Apple, onions
Eqigallocatectin gallate (ECCg)	Green tea leaves
Selenium	Sea Foods
α-Lipoic acid	Yeast, liver
Proanthocyanidines	Grape seeds
Clorogenic & Melanic acids	Coffee beans
Zinc (trace Element)	Liver, egg, spinach

Table 5: Illustrates benefit of CoQ10

Improves NO availability and endothelial function
Improves as well prevents LV Hypertrophy
Decreases inflammatory markers
Improves CVS related QOL (quality of life)

Table 6: Antiaging effects of botanicals [8]

Botanical	Level of Evidence	Potential anti- Aging Effect	Demonstrated anti Aging Effects in Human Studies
Argan Oil	Animal models, human studies	Decrease hyperpigmentation due to tyrosinase inhibition, decreased TEWL, improved elasticity, antioxidant	Decreased TEWL, improved elasticity
Coconut oil	In vitro, animal models, human studies	Emollient, humectant, decreased TEWL, Anti-inflammatory, antioxidant, decrease wound healing, decrease wound healing time, increases collagen	Decreased TEWL, No UV protection
Botanical	Level of Evidence	Potential Anti-Aging Effect	Demonstrated Anti-Aging Effects in Human studies
Soy	In Vitro, animal models, human studies	Antioxidant, increased fibroblast proliferation and increased synthesis of collagen I and III, decreased MMP-1, increased collagen and elastin	Increased Type I and III facial collagen, decreased erythema after UVB exposure, improved facial pigmentation, improved skin texture, reduced fine lines, imporved skin tone
Marigold	In Vitro, animal models, human studies	Antioxidant	Increased Skin Tightness

*Transepidermal water loss (TEWL) MMP

Table 7:

Reduction in the risk of developing ischemic heart disease and other cardiovascular diseases.
Reduction in the risk of developing obesity and diabetes.
Reduction in the risk of developing (and control of) high blood pressure and dyslipidemia.
Reduction in the risk of developing breast and colon cancer.
Hepls in the control of body weight and improves body image.
Tonifiles muscles and preserves or increases muscular mass.
Strengthens bones and joints. Increases coordination and neuro-motor responses; reduces the risk of falls.
Improves immune system activity. Reduces depression and anxiety.
Promptes wellbeing and social integration

metabolism The fundamental role of mTOR signalling in metabolic regulation contributes to the biogenesis and proper functioning of the CV system.

Resveratrol and rapamycin represent the first efforts to translate anti-aging interventions from the laboratory to the clinic, and more studies need to follow . There are strong indications about Resveratrol potential in preventing or retarding the development of HF [52] and it has efficacy of in humans with CVD and H. [10]

1.7.1. Metformin

Emerging evidence suggests that metformin may preserve cognitive function. In the Singapore Longitudinal Aging Study, metformin use was associated with a 51% reduced risk of cognitive impairment. A large observational study of metformin-treated T2DM patients reported lower rates of dementia than in those treated with other diabetes medications. Metformin, which has demonstrated protective effects against several age-related diseases in humans, will be tested in the TAME (Targeting Aging with Metformin) trial, as the initial step in the development of increasingly effective next-generation drugs. [11]

Acarbose (ACA), a drug that blocks postprandial glucose spikes, increases mouse lifespan, we studied ACA at three doses: 400, 1,000 (the original dose), and 2,500 ppm, using genetically heterogeneous mice at three sites In humans, acarbose improves inflammatory markers and reduces cardiovascular events. Consequently, acarbose is of interest in clinical translational aging research since it may influence fundamental processes that contribute to age-related diseases. [12]

1.7.2. Cardioprotective Drugs

The recent research is focussed on identifying novel strategies to recover the damaged and the dysfunctional yet viable myocardium, improve symptomatology and QOL, and prolong survival. These drugs can be able to activate specific protective biomolecules and reduce ongoing damage to the heart and vasculature.

Small studies of L-carnitine supplements soon after a myocardial infarction may be less likely to have another episode, die of heart disease, or develop heart failure, Controlled trials in CVD patients relating to carnitine are needed

The myocardial CoQ10 content tends to decline with age and myocardial dysfunction. A number of controlled trials with supplemental CoQ10 have shown improvements in functional parameters such as ejection fraction, stroke volume and cardiac output. Recently, long-term therapy with CoQ10 has been shown to reduce major adverse cardiovascular events (MACE) and improve HF (Heart Failure) symptoms and found CoQ10 safe and well tolerated

CoQ10 supplementation improves heart and vascular function, reduces atherosclerosis, improves endothelial function, and protects against myocardial damage, CoQ10 formulations are available as either ubiquinol

(reduced form) or ubiquinone (oxidized form). Regardless of whether the formulation contains ubiquinol or ubiquinone, after ingestion CoQ10 appears in the plasma circulation as ubiquinol. Nausea is the most common symptom, followed by allergic maculopapular rash. Caution should be taken in the patients who are on oral anticoagulant therapy.

The cardioprotective effects of HSP70 (Heart shock protein) have been shown in isolated animal hearts after global or regional ischemia. Recently, protection during myocardial ischemia has also been shown for the small heat-shock proteins HSP27 and αB-crystallin.

1.7.3. ACE Inhibitors and ARBs

Angiotensin- converting enzyme inhibition increases of NO production and causes improvement in cardiac function and metabolism and endothelial function. Improvement in cardiac function and metabolism and enhanced endothelial function. Increase in eNOS expression in the heart and carotid artery and marked reduction in tissue ACE expression/activities.

1.7.4. Statins

Inhibition of HMG-CoA reductase Flies Reduction in reactive oxygen specie (ROS) levels in cardiac muscle. Increased NO synthesis and neoangiogenesis in endothelial cells and the central nervous system. The protective effect of statins observed among the very old appears to be independent of Total cholesterol.

1.7.5. Flavonoids

Studies indicate that the flavonoids inhibit platelet aggregation, thrombus formation and coagulation. They reduce oxidative stress, atherosclerosis and arterial blood pressure. They may favorably modify vascular inflammatory and endothelial and capillary function. They may improve lipid profile values and regulate carbohydrate metabolism. The improvement in endothelial function have been observed in CAD patients on daily consumption of flavonoids from purple grape juice (which includes flavan-3-ols, flavonols, proanthocyanidin, and anthocyanins), black tea and flavonolrich cocoa. The flavonoids in red wine (e.g., flavan-3-ols, flavonols, proanthocyanidin, and anthocyanins) improve endothelial function by upregulating endothelial nitric oxide synthase (eNOS) expression and increasing endothelial cell NO production

1.7.6. Phytosterols

The phytosterols also promote general health and well-being and reduce CV risk. The potential action mechanisms of polysulfides in cardioprotection is through hydrogen sulfide releasing activity

Cruciferous vegetables and the Allium family include garlic (Allium sativum) and onion (Allium cepa) and are rich in organopolysulfide as natural donor of H2S.

The saponins in ginseng (triterpene glycosides) are believed to be useful for recovery from ACS/MI

Salvia divinorum (active constituent: a diterpenoid called Salvinorin A) can effectively improve myocardial ischemia and abnormal parameters.[13]

1.7.7. Gene Therapy

First gene therapy successful against aging-associated decline: Mouse lifespan extended up to 24% with a single treatment. The gene therapy consisted of treating the animals with a DNA-modified virus, the viral genes having been replaced by those of the telomerase enzyme, with a key role in aging.Some of the important potential target genes for future gene therapies to retard and reverse CV aging are : Angiotensin-Converting Enzyme (ACE), Growth Hormone/Growth

Hormone Receptor/InsulinLike Growth Factor/Insulin Receptor, Interleukin-21 (IL21), NF-κB: Its inhibition extends life modestly in a number of lower species, given its involvement in immunity, inflammation, apoptosis, and other fundamental processes,

1.7.8. Urokinase (uPA)

The αMUPA mouse lineage has theaddition of a urokinase gene and has a longer life span. Psychotropic drugs and Aged

Elderly patients are particularly vulnerable to adverse effects from neuroleptics, including delirium, extrapyramidal symptoms, arrhythmias, and postural hypotension Advancing age is also associated with increased sensitivity to the central nervous system effects of benzodiazepines.

Reduced b-adrenoceptor function is observed with advancing age. Elderly patients are less sensitive to the chronotropic effect of isoprenaline. Both salbutamol (b2adrenoceptor agonist) and propranolol (badrenoceptor antagonist) show reduced responses with age.[14]

Diabetes in older adults is a growing public health burden. Older adults with diabetes are at increased risk for adverse events from comorbid conditions and polypharmacy. They are also more likely to be

decompensated by an insult from adverse effects of various anti-hyperglycemic agents. Hepatic dysfunction and/or renal impairments in older adults may limit the use of many glucose-lowering agents.[15]

1.7.9. Skin Aging

Alpha Lipoic Acid It is the most potent antioxidant in the market today. It enhances the skin cell metabolism and helps repair aged skin while preventing future damage. With age, glutathione levels naturally decline, making elder person more susceptible to both free radicals and other environmental toxins but lipoic acid tends to restore levels of glutathione, a protective antioxidant, and detoxification compound, to near normal.

Vitamin C (L-ascorbic acid) is a highly water-soluble, sugar-like, low-molecular weight ketolactone. It is a proven anti-wrinkle treatment that works as both a "free radical scavenger" and antioxidant

The lipophilic nature of vitamin E makes it attractive for application to and absorption into skin.

It helps skin repair itself, protects it from harmful bacteria[16]

1.8. Stem cell therapy for promoting healthy brain aging and reversing Alzheimer's disease

The efficacy of intracerebral transplantation or peripheral injection of a variety of stem cells including mesenchymal stem cells (MSCs), NSCs or glialrestricted progenitors (GRPs) has been examined in animal models to improve the function of the aging brain.[17]

1.8.1. Aging Skin

Dermal fillers are soft, gel-like substances that are injected under the skin. They can address a number of common concerns including smoothing of deep under-eye circles, lifting of cheekbones, volumization of the lips, smoothing of lip lines and nasolabilal folds (the creases that run from the side of the nose to the corners of the mouth), and rejuvenation of the hands.

Dermal fillers can be composed of a variety of substances, some naturally occurring and some synthetic. One of the most common compounds used in dermal fillers is hyaluronic acid (HA). HA is a naturally occurring substance found in our skin, and it plays a major role in keeping skin hydrated and volumized. HA fillers, depending on their specific chemical makeup, can last from six months to much longer before being gradually absorbed by the body[18]

Alzheimer's is a type of dementia that affects memory, thinking and behavior.

Symptoms eventually grow severe enough to interfere with daily tasks.

Cholinesterase inhibitors are prescribed to treat symptoms related to memory, thinking, language, judgment and other thought processes. Three different cholinesterase inhibitors are commonly prescribed: • Donepezil (marketed under the brand name Aricept®), which is approved to treat all stages of Alzheimer's disease. • Galantamine (Razadyne®), approved for mild-to-moderate stages. • Rivastigmine

(Exelon®), approved for mild-to-moderate Alzheimer's as well as mild to moderate dementia associated with Parkinson's disease.[19]

1.9. Foods with antiaging properties

Pomegranate seeds are High in vitamin C and have variety of antioxidants. These healthy fruit contain a compound calledpunicalagins, which may help to preserve collagen in the skin, slowing signs of aging.

The orange color of the sweet potato comes from an antioxidant called betacarotene which is converted to vitamin A.

Blueberries are rich in vitamins A and C, as well as an age-defying antioxidant called anthocyanin.

Broccoli has anti-inflammatory activity.

Avocados contain monounsaturated fatty acids & plant sterols- which have heart health benefits.

Many nuts (especially almonds , pecans , walnuts) are a great source of vitamin E, which may help repair skin tissue, retain skin moisture, and protect skin from damaging UV rays. Walnuts evencontainTrusted Sourceanti-inflammatory omega3 fatty acids which can lead to: # strengthen skin cell membranes # protect against sun damage

give skin a beautiful glow by preserving its natural oil barrier

Oily fish are an important source of omega 3- fatty acids which is found both in their flesh and in their skin. Omega 3- fatty acids are polyunsaturated fats that can be used by the body to form anti-inflammatory signaling molecules that can decrease or stop inflammatory responses[20,21]

1.10. Exercise and antiaging properties$

A group of older people who have exercised all of their lives, were compared to a group of similarly aged adults and younger adults who do not exercise regularly. The results showed that those who have exercised regularly have defied the aging process, having the immunity, muscle mass, and cholesterol levels of a young person. Improving one's physical fitness can reduce the risk of death by 44% .In addition, several studies have shown that improving physical fitness has a favorable influence on self image, self-esteem, and depression, as well as anxiety and panic syndromes.

2. Conclusion

The ageing process is characterized by structural and functional changes affecting all organ systems and results

in reduced homeostatic capacity. Nutritional and healthy lifestyle modifications initiated in older human individuals were positively related to reduce mortality risk and delayed deterioration, In aging its impossible to ignore the influence of genetic, epigenetic, psychosocial and environmental factors and their inevitable interaction.

3. Source of Funding

None.

4. Conflict of Interest

None

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