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Physiology of Aging and Mechanism of Herbal Anti-Aging Drugs: A Review from a Pharmaceutics Perspective

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***Abstract*—Aging is a natural phenomenon and is a complex biological process linked with progressive deterioration of physiological functions making body prone to various diseases. Now a days, antiaging is not only limited to prolong lifespan but also emphasizes on healthy and quality life. This has gained the attention of many researchers to develop new antiaging strategies and based on the recent approaches, herbal remedies have proven to be one of the most promising approaches. To understand the functioning of antiaging, it is necessary to understand the physiology of aging. This review explores the key mechanisms of aging and mechanisms of action of herbal anti-aging drugs, focusing on their pharmacological properties and therapeutic potential.**

[1] **Article History**

***Index Terms*—Physiology, Aging, emphasizes, deterioration, telomere attrition**

I. INTRODUCTION:

Aging is can be explained by the gradual deterioration of cellular and tissue function, leading to an increased risk of morbidity and mortality. [1] Aging occurs at cellular level, organ level, tissue level or in whole organism chronologically. [2]It is the process that continues throughout entire life. The study of aging is known as Gerontology.[1] Aging is characterized by genomic instability, telomere attrition (shortened telomere), epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. [3] There are various theories to understand the physiological changes that occurs during aging.

1.1 BIOLOGICAL THEORIES OF AGING

a. **Genetic theory:** This theory states that genes are responsible to determine the lifespan of an individual. It focuses on Telomere (repeated DNA segment at the chromosomal end). The number of repeated segment in telomere determines the lifespan of a cell. Our cells divide continuously and with each division, there is loss of telomeric segment. This is called as telomere shortening. As the telomere shortens to the critical length it stops dividing and ultimately dies. An enzyme, Telomerase prevents the overshortening of telomere. Any mutation in TERC gene (Telomerase RNA component) that encodes RNA segment of Telomerase enzyme leads to the increased rate of aging. These mutaions reproduce at each cell division and leads to the gradual accumulation of mutated cells and impaired functions of cells. [4]

b. **Non Genetic Theories:** These theories consider that the aging occurs due to the molecular and cellular changes. This theory focuses on accumulation of reactive molecules that are generated as the byproduct of cellular activities like cellular respiration. [4], [5], [6]

i. **Wear and Tear Theory:**

This theory assumes that the cells wear and tear out. This theory though does not fit the biological facts as the cells have the potential to repair themselves, but the waste products produced during wear and tear accumulates in the cell and thus interferes with the normal functioning of the cell. [4], [7]

ii. **Cross linking Theory:**

This theory assumes that the cross links occur between the molecules like protein, enzymes alters their shape and structure, which make them unable to carry out normal fuctions. [4], [8]

iii. **Autoimmune Theory:**

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This theory states that, with aging, immune system becomes weaker and looses efficiency leading to autoimmunity (immune system works against owns body), which makes it unable to fight infections and makes body succeptible to age related diseases. [4], [9]

iv. **Oxidative damage Theory:**

Oxidation of cellular molecules makes them highly unstable and reactive which leads to cellular damage. These reactive molecules are called as free radicals. With age, oxidative damages accumulate in the body leading to the oxidative stress. [4]The main molecule that causes oxidation is ROS(Reactive Oxygen Species). This theory later extends to ROS generated in mitochondria which is the energy house of the cell. Mitochondria is unique in having its own DNA and has the potential to repair itself from any damage. Mutation in DNA of mitochondria impairs protein function in mitochondrial respiration machinery. This enhances the production of damaging free oxygen radicals. Accumulation of mutation in mitochondrial DNA leads to the mitochondrial dysfunction. [10], [11]

2. **PATHOPHYSIOLOGY OF AGING**

a. **Genomic Instability**

To maintain the normal growth, and repair of our tissue, most of our undergo cell division. Normally, cell division starts with DNA replication and then the cell splits into two to form two daughter cells. During the DNA replication, DNA damage is checked at various checkpoints and various surveillance mechanism works in order to assure that the DNA that is copied is exactly the same as original. [4], [12] This surveillance mechanism includes the formation of tumor suppressor gene and DNA repair gene to fix the errors that occur during cell division. Any defect in surveillance mechanism or checkpoints leads to the genetic instability. Any toxic substance or disease that induces mutation results in DNA damage. With growing age, DNA surveillance mechanism becomes less effective, leading to the persistent DNA damage, which triggers senescence. The common factors which trigger genetic instability are: oxidative stress, environmental factors, or an error in DNA replication. [12], [13], [14]

b. **Telomere Attrition**

Telomeres are the specific protein structure found at both the ends of chromosome. The main function of telomere is to safeguard genome from degradation, unwanted recombination, repair or any interchromsomal fusion. Normally, a small part of telomere is lost during each cell division. When the length of telomere reaches its critical limit, the cell enters senescence or apoptosis. [15]

Telomere attrition is a key driver of cellular aging and has been associated with age-related diseases. The length of the telomere may act as the biological clock to know the lifespan of the cell. Some agents related to specific lifestyles may accelerate the shortening of telomere by inducing DNA damage at telomeric end. This ultimately affects the lifespan and induces aging. [16]

II. Epigenetic Alterations

Gene expression is altered by several other factors like lifestyle, environmental factors, behavioural changes, and psychological condition of an individual. These factor are refered to as the epigenetic factor. [17]Epigenetic changesdo not alter the DNA sequence but influence gene expression by DNA methylation, histone modification, and chromatin remodeling. Though epigenetic changes are reversible but these changes contributeto cellular aging and disease progression. [6], [18]

A. Loss of Proteostasis

Proteostasis is the complex connection of pathways that regulates the synthesis, folding and degradation of protein to maintain the normal health of cell and organism. There are numerous mechanism that contribute to proteostasis. Reduced levels of soluble chaperones (functional group of proteins) and disruption of protein degradation pathways leads to the disturbance in protein homeostasis. [19]HSP70, HSP40/DNAJ and co-chaperones ensure proper folding of proteins accumulation of misfolded and damaged proteins. On misfolding of protein, chaperones either refolds substrate or directs them to proteosomes for degradation. [20] Decreased level of chaperones impairs Clathrin-mediated endocytosis (CME) leading to misfolding of protein and its aggregation thereby resulting in loss of proteostasis. [21]

B. Mitochondrial Dysfunction

Mitochondria are essential for energy production and regulation of cellular metabolism.Any abnormalities in mitochondrial function leads to aging through following mechanism:

- **Mutations in Mitochondrial genome and mitochondrial dynamics:**

Mitochondria is a unique organelle as it contains its own genome mtDNA. Aging with time results in accumulation of mtDNA mutations mainly due to errors during DNA replication or repair of damaged DNA. The most frequent

type of mutations that occur in mitochondria are point mutations and deletions. Mutaions in DNA leads to abnormalities in Electron Transport chain, enhanced oxidative damage at cellular level. Moreover, neurons with COX deficiency also increases resulting in the loss of COX activity thereby affecting normal physiology of organs. Mitochondrial dysfunction is also related to various aging pathologies like diabetes, Cardio Vascular Disorders, Neurodegenerative disorder. [22] Therefore there must be proper regulation between production of mitochondria and degeneration of damage mitochondria to maintain proper cellular homeostasis. Fission and fusion of mitochondria leads to altered mitochondrial dynamics thereby inhibiting mitophagy. This leads to the accumulation of damaged mitochondria. Furthermore, disturbed mitophagy also prevents the clearance of dysfunctioned mitochondria causing cellular deterioration. [22], [23]

• **Oxidative stress caused by Reactive Oxygen Species:**

Oxidative metabolism leads to the production of Superoxide anion, hydrogen peroxide and hydroxyl free radicals. Superoxide anions is converted into hydrogen peroxide by uperoxidedismutases. Through Fenton reaction, this hydrogen peroxide in presence of reduced transition metals, gets converted to highly reactive hydroxyl free radical also known as ROS. ROS thus produced causes cellular damage by oxidizing lipids, nucleic acid and proteins. [10]

III. Cellular Senescence

Cellular senescence is a state of irreversible cell cycle arrest that occurs in response to cellular stress or damage.

• **Tumor suppressor pathways and senescence:**

Tumor suppressor pathways P53and P16/RB plays the key role in cell cycle arrest. Telomeric attrition, oxidative stress cause DNA damage and damage to DNA leads to increased γH2Ax and 53BP1 deposition in chromatin. This deposition activates kinase cascade leading to the activation of p53 cytochrome. p53 induces, transcription of p21which is a cyclin-dependent kinase inhibitor and blocks CDK4/6 activity. This results in in hypophosphorylatedRb and cell cycle exit. Although slight increase in p53 level, cell can undergo quiescent state and DNA repair process gets activated, but sustained increase in p53 level leads to the permanent arrest of cell cycle. [24]

• **Senescent cells secrete pro-inflammatory and senescence:**

SASP is involved in many functions attributed to senescent cells. SASP recruits the immune system to eliminate senescent cell. It also activate the adaptive and innate immunity. In adverse conditions, SASP activates tumor suppressor mechanism. But SASP mediated recruitment of immature myeloid cells has immune suppressive effects on prostate and liver cancer, In addition SASP promotes angiogenesis and thus stimulate tumerogensis. This contributes to the tissue dysfunction and inflammation. [24], [25]

IV. Stem Cell Exhaustion

Stem cells are long living cells that can undergo self regeneration and can differentiate to produce matured daughter cells. These cells are responsible for tissue regeneration and repair process. With aging, stem cell function declines, leading to impaired tissue homeostasis and regenerative capacity.[26]Proteostasis, mitochondrial dysfunction, DNA damage, Extracellular signaling and epigenetic remodeling are the main causes of Stem cell exhaustion. [26], [27]

V. Altered Intercellular Communication

Aging is associated with changes in intercellular communication, including increased pro-inflammatory signaling and disruption of tissue homeostasis. Chronic inflammation, also plays vital role in aging. [28] [29], [30], [31], [32], [33], [34]

3. POTENTIAL ANTIAGING HERBS:

We cannot stop the process of aging but we can delay the onset of aging by using different herbs.The potential antiaging herbs along with their mode of action are discussed below in Tables I and II .

4. CONCLUSION :

Aging is a natural process which can be described as deterioration of cellular and tissue functions, making body prone to various diseases. Aging can be characterised by Genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered inter cellular communication [35], [36], [37], [38], [39], [40], [41], [42], [43] .

As per the recent studies, many plant species are found to be effective for delaying the onset of aging and age related diseases. This review was aimed to study some important herbs along with their pharmacological action, out of which few important herbs are Green tea (improves genomic instability, prevents telomere shortening, antioxidant activity), Korean Ginseng (Antioxidative, Antiinflammatory, upregulates telomerase activity and DNA repair mechanism, Stimulates the proliferation and differentiation of mesenchymal stem

TABLE I
ACTIVE CONSTITUENTS AVAILABLE IN HERBS WITH THEIR MODEOF ACTION. (A)

Herbs	Active Constituents	Mode of Action
Green Tea/ Camellia Sinensis	Polyphenols, Catechin, Epigallocatechin, vitamins and minerals	Improves genomic instability and prevents telomere shortening, Antioxidant activity(29,30)
Monk Fruit/ Siraitiagrosuenorii	Mogrosides	Increase Telomerase Length, Acts as Antioxidants(31,32)
Cat's Claw/ UncariaTomentosa	Proanthocyanidin	Improves genomic instability and prevents telomere shortening, Reduces brain plaques, thereby reducing brain aging. (30,33)
Korean Ginseng/ PanaxGinseng	Gintonin	Antioxidative, Antiinflammatory, upregulates telomerase activity and DNA repair mechanism, Stimulates the proliferation and differentiation of mesenchymal stem cells, improves tissue repair and regeneration. (34)
Vanilla Planifolia/ Vanilla	Vanillin	Decreases DNA damage and oxidative stress (Antioxidant). (35)
Maidenhair Tree/ Ginkgo biloba	Flavonoids and terpenoids	Antioxidant, Scavanges free radicals and upregulates endogenous enzymes, Promotes neural stem cell proliferation and differentiation. (36)
Turmeric (Curcuma longa)	Curcumin, Contains anti-inflammatory effects	Inhibits the NF-κB signaling pathway, reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. (37)
Boswelliaserrata	Boswellic acids	Inhibits 5-lipoxygenase and reduce the production of leukotrienes, thus exerting antiinflammaory action. (38)
Ashwagandha (Withaniasomnifera)	Alkaloids, steroidal lactones and saponins	Reduces cellular senescence and promotes cell viability. (39)
Golden root/ Rhodiolarosea	Rosin, rosavin, rosari and salidroside	Enhances Mitochondrial Function
Gotu Kola (Centellaasiatica)	Assiaticosides, terpenoids, saponins	Promotesproteostasis by promoting the expression of heat shock proteins (HSPs), which assist in proper protein folding and prevent aggregation. (40)
Glycirhiza Glabra	Glycirhizin	Enhances proteasome activity and autophagy, facilitating the degradation of damaged proteins. (41)

TABLE II
ACTIVE CONSTITUENTS AVAILABLE IN HERBS WITH THEIR MODEOF ACTION. (B)

Milk Thistle/ Silybummarianum	Silymarin	Enhances proteasome activity and autophagy, facilitating the degradation of damaged proteins.(42)
Hypericum	Hypericin	Enhances proteasome activity and autophagy, facilitating the degradation of damaged proteins
Chinese Foxglove/ RehmanniaGlutinosa	iridoids, phenethyl alcohol glycosides, terpenes, terpenes and fatty acids.	Maintains cell cycle (Quiscent state), Antioxidant activity
Wolfberry/ Lycium barbarum	carbohydrates	Decreased cell death (43)
Cofee/ Coffee Arabica	Chlorogenic acid, condensed proanthocyanidins, Quinic acid, and Ferulic acid	Antioxidant(42)
Grapes/ V. Vinifera	Proanthocyanidins	Antimutagen, Antioxidant, Antiinflammatory(42)
Green Tea/ Camellia sinensis	catechin, gallaogatechin, epicatechin, epigallocatechin, epicatechin gallate, and apigallocatechin gallate	Antiinflammatory, Suppresses the Age-Related Increase in Collagen Crosslinking.(42,43,44)
Pomegranate/ punica Granatum	Catechin	Protects from UV, Relieves oxidative stress(45,46,47)
Soybean	Isoflavones	Antiphotoageing
Kacip Fatimah/ Labisia pumila	quercetin, myricetin, kaempferol, naringin, rutin, apigenin, anthocyanins, catechin, epigallocatechin	Antioxidant
Amla/ Emblica Offinales	Ellagic acid, Gallic acid, Emblicanin A & B, Phyllembein, Quercetin, and Ascorbic acid	Antioxidant(47,48)

cells [44], [45], [46], [47] , improves tissue repair and regeneration), Gingko Biloba (Antioxidant, Scavanges free radicals and upregulates endogenous enzymes, Promotes neural stem cell proliferation and differentiation), Glycirrhiza Glabra (Enhances proteasome activity and autophagy, facilitating the degradation of damaged proteins), Milk Thistle (Enhances proteasome activity and autophagy, facilitating the degradation of damaged proteins). [48]

Additional Information

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