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Understanding the Multifaceted Process of Aging: Theories, Mechanisms, and Implications for Treatment

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ABSTRACT: The aging process is a multifaceted biological phenomenon characterized by alterations at the molecular, cellular, and organ levels that culminate in a gradual, unavoidable, and unavoidable reduction in the body's capacity to react suitably to internal and/or external stimuli. Aging is a complex process that involves different mechanisms as The "Wear and Tear" Theory ,The Genetic Control Theory ,The Neuroendocrine Theory ,Waste Accumulation Theory ,Divisions Theory, Autoimmune Theory, Thymic-Stimulating Theory ,Mitochondrial Theory Mitochondria, Errors and Repairs Theory, Redundant DNA Theory Cross-Linkage Theory , Death Hormone Theory (DECO), Caloric Restriction Theory ,The Rate of Living Theory ,Gene Mutation Theory, Accumulated mutations Theory, Theory, Order to Disorder Theory, Disposable soma Theory, Antagonistic pleiotropy theory, The Telomerase Theory ,The free radical Theory. The two main categories of aging theories that explain cellular aging are structural damage and programmed theories. Different types of cells experience physiological stressors due to a range of circumstances. Notably, post-mitotic and mitotic cells have different capacities for proliferation and age differently in response to these pressures through different processes of cellular senescence and death, respectively. Over time, these aging cells build up and eventually cause old tissues to malfunction. The aim of this review is to throw light upon the effected of aging and who to treatment it.

Keywords: cellular aging, aging, senescence, DNA Damage, gene mutations , free radical

1. INTRODUCTION

A cell's senescence is a defense system that prevents it from suffering needless harm. Cellular senescence is the process of aging cells. The senescent state is characterized by resistance to cell death, an elevated secretory phenotype, and the inability to reenter the cell cycle after mitogenic stimulation. Many physiological and pathological events, including tissue remodeling, damage, cancer, and aging, cause many tissues to undergo senescence [1]. Senescent cells can have beneficial effects even though they are one of the aging process' driving forces and the cause of many illnesses associated with aging [2]. Senescent cells are necessary for tissues to heal and for the correct development of the embryo during tissue remodeling and embryogenesis. Aging is a strong barrier to stopping the growth of new tumors in cancer [3]. Thus, several study areas are beginning to take a closer look at the discovery and characterization of important aspects of senescence, the induction of senescence in cancer cells, or the removal of senescent cells in aged tissues using medications. We outline the essential senescence characteristics here, including the cell-autonomous and noncell-autonomous [4]. About the surrounding cells, the aging cell is bigger. Cells that are older stop dividing. Aging cells can make mistakes during cell division, which might damage the surrounding tissues or the cells themselves. A normal cell can become a senescent, aged cell in around six weeks [5].

2. History of cellular aging

Diploid cells experience cellular senescence, a durable cell cycle halt that shortens the cells' proliferative life span. Human diploid fibroblasts in culture were shown to be able to divide their cells up to a specific number before halting, a phenomenon that was first reported by Hayflick and Moorhead in the 1960s. The gradual shortening of telomeres

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with each cell division causes this biological clock, sometimes referred to as the "Hayflick limit," which is a physiological reaction to prevent genomic instability and the consequent buildup of DNA damage [3].

3. Causes of Cellular Aging

1- DNA Damage: Chromosomes are a component of every cell, and all of the genetic information is included in these chromosomes. A telomere is the name for the end of these chromosomes. The telomere shortens following every replication cycle. Cell replication is chaotic and hazardous in the absence of telomere. DNA damage can be caused by ultraviolet radiation, or UV radiation. Thus, to preserve the genetic information, cells are modified [4].

2-Oxidative Stress: Replication mistakes may result from reactive oxygen species present in a cell's environment. Such reactive oxygen species cause cellular replication to stop. Cell aging is initiated by oxidative stress [5].

3-Decreased Autophagy: The meaning of Autophagy is a mechanism that destroys itself. As a cell matures, it breaks down into its constituent parts. Autophagy is the process by which a cell breaks down its products. Lysozymes are digestive enzymes that make up a cell. These lysosomes are in charge of disassembling harmed cell components. This inhibits the cell's capacity for replication and raises its protein content. Aging is brought on by this mechanism. [6,7]. Fig 1

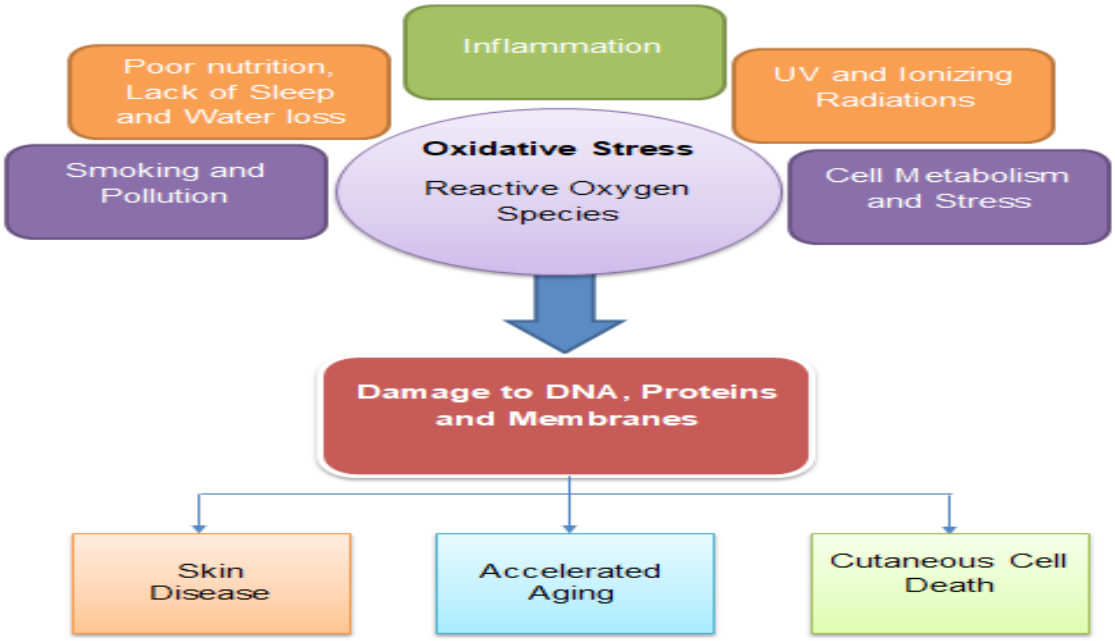

FIGURE 1. - Causes of aging [7]

4. Prevent Cellular Aging

Although we can't halt aging entirely, we can certainly slow it down. The strategies we can use are as follows:

• A nutritious and well-balanced diet is beneficial in preventing injury and promoting healing [8].

• Stress Management: Reducing stress hormones can be achieved by practicing yoga, meditation, and engaging in hobbies [8].

• Exercise: According to Gregory et al. [9], consistent exercise combined with lifestyle changes protects against chronic illnesses and helps to develop robust cells and tissues.

• Prevent Contact with the Triggering Agents: Aging can be controlled by wearing protective clothing, and limiting exposure to the sun, and other environmental factors [7].

• Prevention Is Better Than Cure: Regular visits with the doctor and proper weight, food, and blood pressure management decrease the risk factors [10].

5. Theories of cellular aging

5.1 The "Wear and Tear" Theory

It was in 1882 when German biologist Dr. August Weismann first proposed this idea. He thought that misuse and abuse caused harm to the body's cells. Toxins in the environment and food wear down the skin and organs. Organ wear and tear are not the only places it occurs; cells are also affected [11].

5.2 The Genetic Control Theory

According to this hypothesis, each human is born with a distinct genetic code, a predisposition to specific forms of both mental and physical abilities and a genetic inheritance that greatly influences how fast and how long a person lives. Every individual has a biological clock. The bodies begin to age and eventually die as that clock strikes twelve. Nevertheless, there is a great deal of diversity in the timing of this genetic clock based on factors such as development and real lifestyle (quality of life, food, cleanliness, medical practices, etc.) [12]. Fig 2

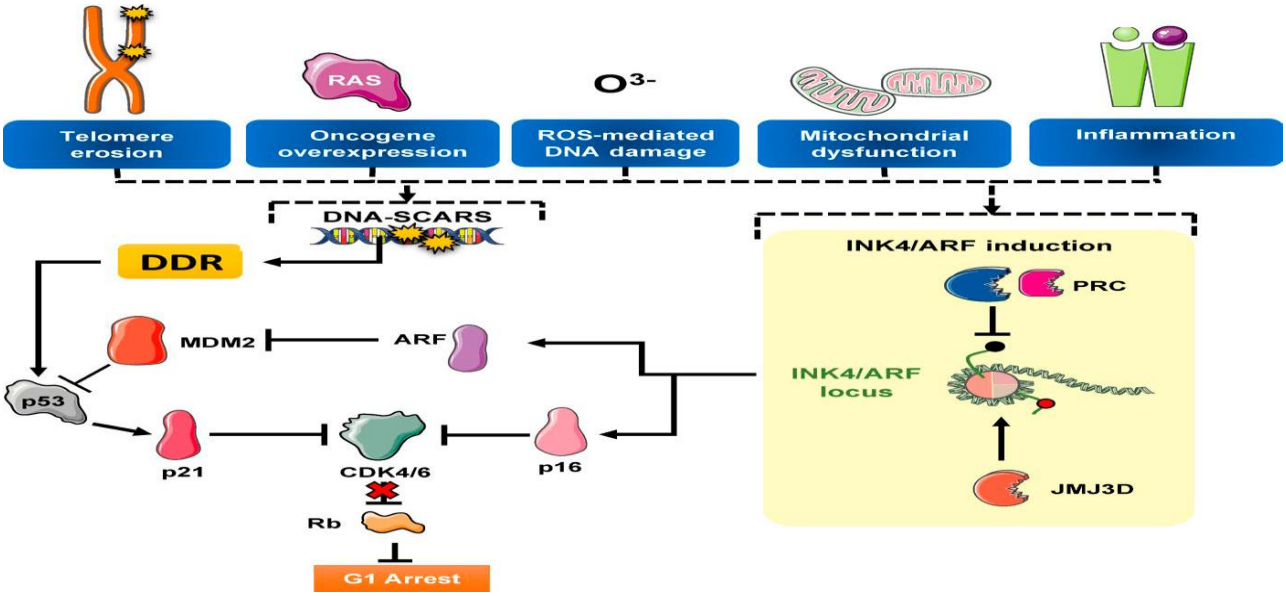

FIGURE 2. - pathways controlling arrest induced by senescence

The two primary mechanisms that control the senescence growth arrest are p16INK4a/Rb and p53/p21CIP1, both of which lead to the regulation of CDK4/6. Polycomb repressive complexes (PRCs) often quiet the INK4A/ARF gene, which is activated during senescence. DNA segments with chromatin changes that reinforce senescence and are repair-resistant trigger the DNA damage response (DDR), which in turn activates the p53/p21CIP1 pathway (DNA-SCA RS) [4].

5.3 Limited Number of Cell Divisions Theory

Waste materials inside the cell build up and have a direct impact on how many times it divides. Cell deterioration occurs more quickly the more waste amassed over time [12].

5.4 Hayflick Limit Theory

In 1962, two of the greatest names in cellular biology history, Drs. Hayflick and Moorehead, showed that grown human cells could age. According to Hayflick's theory, every living cell has a biological clock that regulates the aging process. According to the 1961 research, human cells only live for a certain amount of time. The genetic material, membranes, and cell organelles all underwent the most noticeable alterations. The aging process may be brought on by aberrant cell function and tissue and organ cell loss [13]. Fig 3

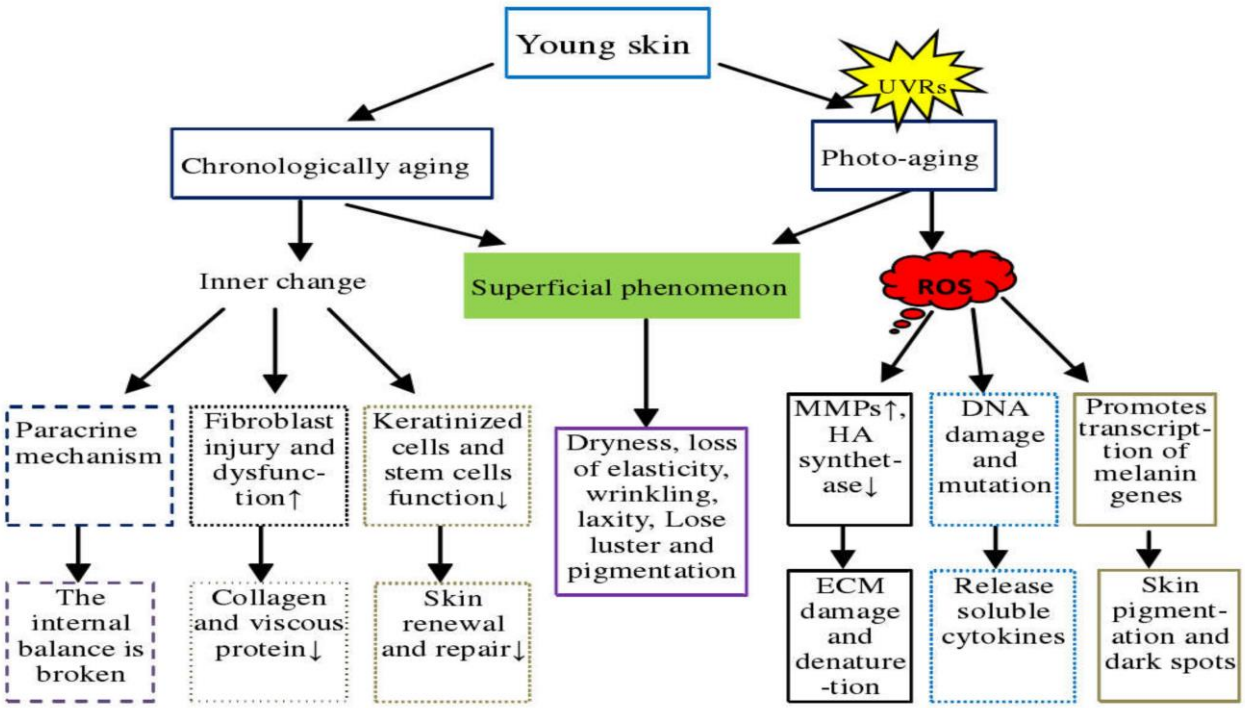

FIGURE 3. - Comparing the effects of photoaging on the skin with chronological aging

5.5 Death Hormone Theory (DECO)

Neurons in the brain don't proliferate like other cells do. Approximately 10 percent of individuals die over their lifetime, from a starting population of about 12 billion. Per Dr. Denckle's conjecture, the pituitary secreted DECO (decreasing oxygen consumption hormone sometimes known as "death hormone") as people aged. By doing this, the pace at which cells turn food into energy is slowed down—a process known as thyroxine utilization [12]. assert that an increase in metabolic rate hastens the aging process.

5.6 Thymic-Stimulating Theory

According to this hypothesis, the immune system of the body is weakened as a result of the thymus' absence, which accelerates the aging process. Thymic hormones possibly be the primary regulators of immunity since they stimulate and regulate the synthesis of neurotransmitters, brain, and endocrine system hormones. At birth, this gland weighs 200–250 grams; by the time it reaches 60 years old, it only weighs around three grams. According to Goldberg et al. [14], thymic factors can assist in revitalizing elderly people's weak immune systems and rebuild the immune systems of newborns born without them.

5.7 Mitochondrial Theory

The directed experimental findings of mitochondrial aging are consistent with the free radical theory. They create potentially harmful free radicals in the process of producing cell energy. Due to their absence of most of the protections present in other cell components, mitochondria are also among the most vulnerable to damage by free radicals [15,16,17]. Fig 4

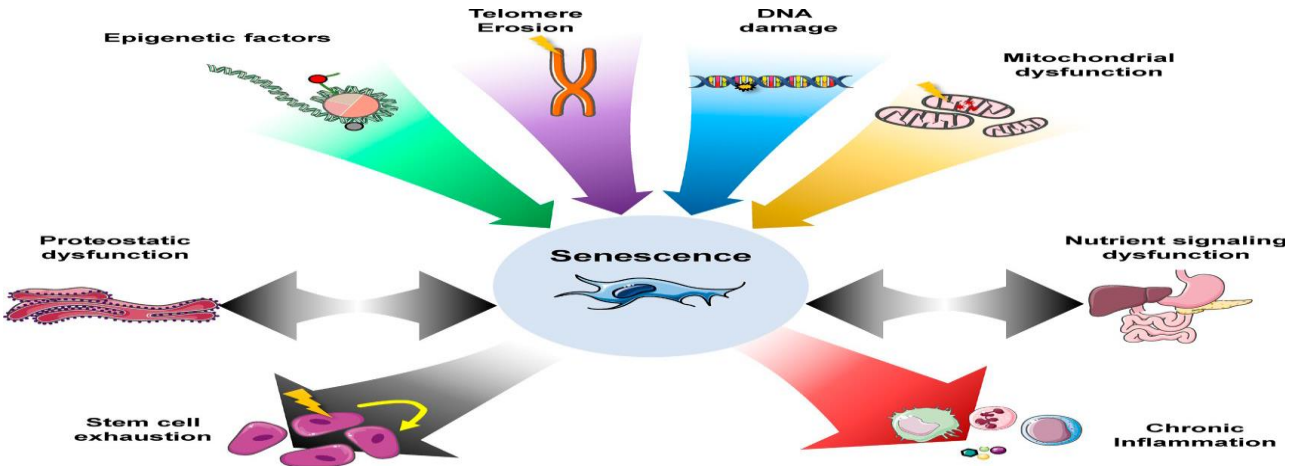

FIGURE 4. - Senescence is a key indicator of aging

The main causes of damage during aging include DNA damage, telomere damage, mitochondrial malfunction, and epigenetic dysregulation. Senescence can be brought on by a number of these damage-causing factors. Senescence itself can cause persistent inflammation and stem cell depletion, two hallmarks of aging that result from damage. The senescence response is closely associated with other damage-related reactions, including proteostatic dysfunction and alteration of nutrition signaling [4].

5.8 Errors and Repairs Theory

According to Dr. Leslie Orgel's 1963 suggestion, "an error in the machinery for making protein could be catastrophic." Sometimes errors occur in the replication of DNA and the creation of proteins. Because the body's DNA is so important, when a mistake is made, the body's natural repair mechanisms take over. However, the system is not able to fix these defective molecules perfectly every time, and the build-up of these damaged molecules can lead to illnesses and other age-related changes [18].

5.9 Redundant DNA Theory

This idea explains age changes as the result of mistakes building up in the DNA. However, when these mistakes mount up, this hypothesis also assigns blame to the backup genetic patterns made up of the same DNA that take over until the system breaks. According to Dr. Zhores Medvedev, the extent to which certain repetitive gene sequences may determine how long a species lives [12].

5.10 Cross-Linkage Theory

Johan Bjorksten initially suggested the concepts of cross-linking and developmental aging in 1942. He used this idea to explain immune system deterioration, aging disorders including sclerosis, and skin elasticity loss. One of the most prevalent proteins in bone, cartilage, ligaments, tendons and skin is collagen. A ladder with few rungs on its legs are comparable to collagen protein. Extra rungs provide a cross-link between every protein and its surrounding neighbors. Young individuals have few cross-links and unrestricted upward and downward movement of the ladders. Collagen maintains its pliability and softness. These cross-links are assumed to start preventing waste and nutrients from moving freely between cells. It seems that cross-linking also happens when immune systems that are older are unable to remove too many glucose molecules from the blood. Destructive free radicals are created when these sugar molecules interact with proteins, creating cross-links [18].

5.11 Autoimmune Theory

The body's capacity to create the essential antibodies to combat illness and to discriminate between proteins and antibodies both deteriorate with age. The immune system, in a way, turns against itself and becomes destructive. Lupus, scleroderma, and adult-onset diabetes are a few autoimmune diseases [12].

5.12 Caloric Restriction Theory

Dr. Roy Walford has put forth the hypothesis of calorie restriction or energy limitation. He created a low-calorie, high-nutrient diet to show how "undernutrition with malnutrition" may significantly slow down the aging process, at least in terms of function. Under this method, a person would progressively lose weight until they reached a position where their metabolism was optimized for optimal health and longevity. Along with the high-low diet, Walford emphasized the value of modest vitamin and mineral supplementation and frequent exercise [19].

A primary neuroendocrine consequence of caloric restriction is the arcuate nucleus's production of neuropeptide Y. Neuropeptide Y is believed to have functions in the regulation of behavioral processes such as anxiety, learning, and memory, in addition to its appetite-stimulating effects. Studies indicate a mechanistic distinction between the two when it comes to behavior, calorie restriction has been shown to have impacts on arcuate nucleus signaling [20].

5.13 The Rate of Living Theory

Dr. Max Rubner, a German scientist, first proposed this idea in 1908 and discovered the link between body size, longevity, and metabolic rate. All it says is that everyone has a certain quantity of energy at birth. Aging will occur more slowly if this energy is used carefully. Aging occurs faster if energy is spent quickly. According to Bengtson and Schaie [12], Alternative theories of pace of living focus on restricting variables like the quantity of oxygen breathed or the number of heartbeats.

5.14 Gene Mutation Theory

Researchers began looking into how mutations affect aging in the 1940s. Genes, which are essential to life, can undergo mutations. Radiation experiments were used to validate this idea. Radiation was found to hasten an animal's aging process in addition to increasing gene mutation. Subsequent investigations revealed, however, that the alterations brought about by radiation were only imitating aging changes. According to Warner et al. [11], the hypothesis's validity was further undermined when it was shown that rats exposed to moderate levels of radiation saw an increase in lifespan.

5.15 Accumulated mutations theory

In 1952, Medawar made the initial suggestion. Natural selection has a decreasing effect as people age, according to this idea. Because a harmful mutation affecting the fitness of a significant portion of the population will be affected, there will be substantial selection pressure to eradicate it when it first appears. Many others with the same mutation will have passed away before it is expressed if it does not show symptoms until later in life. Natural selection has less chance of eliminating a mutation from the genome if it is infrequently expressed. As a result, the mutation may accumulate in the genome and be transmitted down from one generation to the next [21].

5.16 Antagonistic pleiotropy theory

The second evolutionary explanation of aging is antagonistic pleiotropy. Williams developed the theory in 1957, arguing that there are genes that have advantageous early effects but detrimental consequences later in life. Despite the possibility that these genes might eventually lead to senescence, they would be chosen if they improve reproductive success in the early stages of life [21].

5.17 Disposable soma theory

Maintenance of cells is expensive. It would seem senseless to expend valuable metabolic resources to keep the soma alive over the organism's anticipated lifespan, as extrinsic mortality is quite high in the environment. From an evolutionary perspective, it will be more advantageous to spend extra energy to raise the reproductive capability since it will improve that individual's fitness.

to sustain the soma long enough for reproduction, an organism must use a certain amount of energy, but not as much as would be needed to maintain it eternally, as a result of evolutionary processes.

Variations in life lengths among animals can be partially explained by the disposable soma idea. According to Sorouu and Seymour [21], greater effort should be put into procreating as frequently as feasible when a species' extrinsic mortality rate is greater.

5.18 Order to Disorder Theory

Human bodies go through an orderly system from conception to sexual maturity. Humans focus most of their energy on carrying out a genetically predetermined blueprint for the systematic synthesis and organization of a vast array of different kinds of molecules, according to Dr. Leonard Hayflick. However these energies begin to lose some of their effectiveness during sexual maturity. Errors are generated by other molecules when molecules are disorganized, and so forth. Aging results from these uncontrollably changing cells, tissues, and organs. Because everyone is different when it comes to disorderliness, tissues and organs may degenerate at varying speeds [12].

5.19 The Telomerase Theory of Aging

The rapid advancements in genetics and genetic engineering technology gave rise to this notion. Telomeres are nucleic acid sequences that protrude from the ends of chromosomes. The purpose of telomeres is to keep chromosomal

integrity intact. Telomeres get shorter with each cell division, which causes cellular damage and aging-related cellular death [22, 23].

The enzyme telomerase, which is exclusive to cancer and germ cells, is necessary to repair the telomeres that are breaking down [24]. The "clocking" process that regulates the life span of dividing cells appears to be altered by telomerase. It seems to replenish and repair the telomeres [25, 26, 27].

5.20 The free radical theory

According to this theory, aging can be reversed by strengthening the antioxidant defense system to lessen damage caused by free radicals. The free radical hypothesis is one of the many hypotheses explaining the aging process. It suggests that the harmful effects of free radicals cause the functional decline linked to aging. This idea has drawn a lot of attention.

It is difficult to construct a universal theory since age-related changes in humans are not uniform and are instead impacted by both genetic and environmental factors. The fact that there is a worldwide aging is universal. One may ultimately learn that there is no upper limit to the length of human life through theoretical gerontology and anti-aging treatment (26). According to some research, aging causes the antioxidative defense system to be suppressed and lipid peroxidation products to accumulate. On the other hand, ginsenoside-Rd reduces oxidative damage, which may be the cause of the GSH/GSSG redox status intervention [28].Fig 6

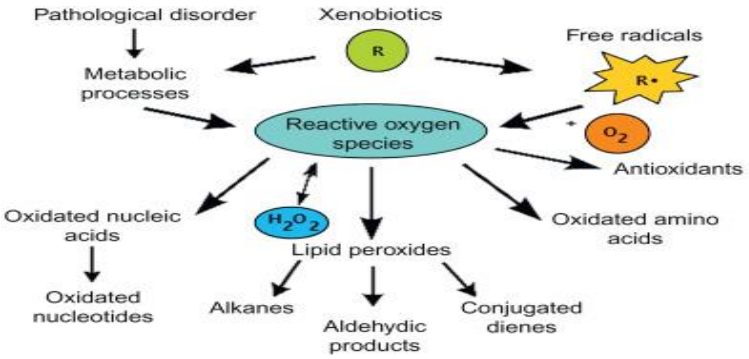

FIGURE 5. - free radicals effect [5]

6. CONCLUSION

Cells that are getting older cease to divide; they also regulate cell division, guard against tumor development, and transition into senescence following injury. It can be brought on by autophagy, oxidative stress, or damage to DNA. Cellular aging has a major effect on age-related diseases.

Environmental and genetic variables both have an impact on the intricate and protracted biological process of aging. While there are some therapeutic benefits associated with stem cell transplantation, hyaluronic acid injection, and retinoic acid injection, there are drawbacks to each approach, with the improvement in people's expectations regarding the effectiveness, safety, and durability of treatment approaches, have turned from aging via nutritional control into an inevitable trend.

In addition to chronic inflammation, oxidative stress has been linked to a number of chronic illnesses, including frailty and sarcopenia in the elderly. Oxidative stress biomarkers might be a helpful tool for diagnosis or a target for treatment. The combined effects of moderate aerobic exercise and antioxidant treatment, including resveratrol and other dietary substances, may mitigate the clinical damage caused by oxidative stress.

Even while sunlight is good for us and necessary for life, too much exposure to it can have negative health impacts, such skin cancer. Instead of constantly reapplying topical sunscreen, studies and research have been done to provide sunscreen in the form of tablets for oral administration.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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