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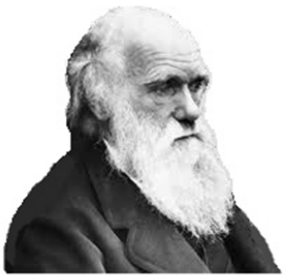

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Involvement of Free Radicals in the Ageing of Cutaneous Membrane

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ABSTRACT

The free radical theory of aging suggests that aging is caused by accumulation of damage inflicted by reactive oxygen species (ROS). However, this concept has been very useful in defining the contribution of oxidative damage to the aging process, an increasing number of studies opposes it. The idea that oxidative damage represents only one of many causes of aging also has limitations, as it does not explain causal relationships and inevitability of damage accumulation. Here, it is discussed that heterogeneity, infidelity and imperfectness of each and every biological process may be responsible for the inevitable accumulation of by-products and other damage forms. Although ROS are prototypical by-products, their contribution to aging is governed by the metabolic organization of the cell, its protective systems, and genotype. These factors are controlled by natural selection, dietary and genetic interventions that extend lifespan, change the composition of cumulative damage and the rates of accumulation of its various forms. Oxidative damage, like other specific damage types viewed in isolation or in combination, does not represent the cause of aging. Instead, biological imperfectness, which leads to inevitable accumulation of damage in the form of mildly deleterious molecular species, may help define the true root of aging. Free radical and other specialized damage theories served their purpose in the understanding of the aging process, but in the current form they limit further progress in this area.

***Keywords*:** Cutaneous membrane, Reactive oxygen specie (ROS), Free radicals, Ageing, Antioxidant

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1. INTRODUCTION

Skin is a layer of usually soft and flexible outer tissue covering the body of a vertebrates, the skin has three main functions which are for: protection, regulation, and sensation.

Other animal coverings, like the arthropod exoskeleton, have different developmental origin, structure and chemical composition. The word cutaneous means "of the skin" (from Latin cutis 'skin'). In mammals, the skin is an organ of the integumentary system made up of multiple layers of ectodermal tissue, and protects the underlying muscles, bones, ligaments and internal organs. Skin differently exists in amphibians, reptiles, and birds [1]. Skin (including cutaneous and subcutaneous tissues) plays an important role in formation, structure and function of extra-skeletal apparatus such as horns of bovid (for example, cattle) and rhinos, cervids' antlers, giraffids' ossicones, armadillos' osteoderm, and penis/ clitoris [2].

All mammals have some hair on their skin, even marine mammals like whales, dolphins, and porpoises which appear to be hairless. The skin interfaces with the environment and is the first line of defense from external factors. For example, the key role of the skin is to protect the body against pathogen [3] and excessive loss of water [4]. Other skin functions also include insulation, temperature regulation, sensation, and the production of vitamin D folates. Severely damaged skin may heal by forming scar tissue. This is sometimes discolored and depigmented. The thickness of skin also differs from location to location on an organism. In humans for example, the skin located under the eyes and around the eyelids is the thinnest skin in the body at 0.5 mm thick, and is one of the first areas to show signs of aging such as wrinkles. The skin on the palms and the soles of the feet is 4 mm thick and is the thickest skin on the body. The speed and quality of wound healing in skin is caused by the reception of estrogen. [5]

The word skin referred to dressed and tanned animal hide and the usual word for human skin was hide. The skin and its appendages (nails, hair and certain glands) form the largest organ in the human body, with a surface area of 2 m^2 [6]. The skin makes up 15% of the total adult body weight; its thickness ranges from less than 0.1 mm at its thinnest part (eyelids) to 1.5 mm at its thickest part (palms of the hands and soles of the feet) [7].

2. THE STRUCTURE OF THE SKIN

The skin is divided into several layers, as shown in Figure 1. The epidermis is mainly made up of keratinocytes. Under the epidermis is the basement membrane (also known as the dermo-epidermal junction); this narrow, multilayered structure holds the epidermis to the dermis. The layer below the dermis, the hypodermis, is largely made of fat. These structures are described below (**Figure 1**).

2. 1. Epidermis

The epidermis is the outer layer of the skin, which is defined as a series of secretive layer of cell found in the uterus, parts of the anus and eye, the male urethra, the vas deferens and in the part of the pharynx, primarily making up keratinocytes in progressive stages of differentiation [8]. Keratinocytes produce the protein called ‘keratin’ and are the major building blocks of the epidermis. As the epidermis contains no blood vessel, it entirely depends on the underlying dermis for nutrient delivery and waste disposal through the basement membrane.

The main function of the epidermis is to act as a physical and biological barrier to the external environment and also preventing penetration by irritants and allergens. At the same time, it prevents the loss of water and maintains internal homeostasis [10,11].

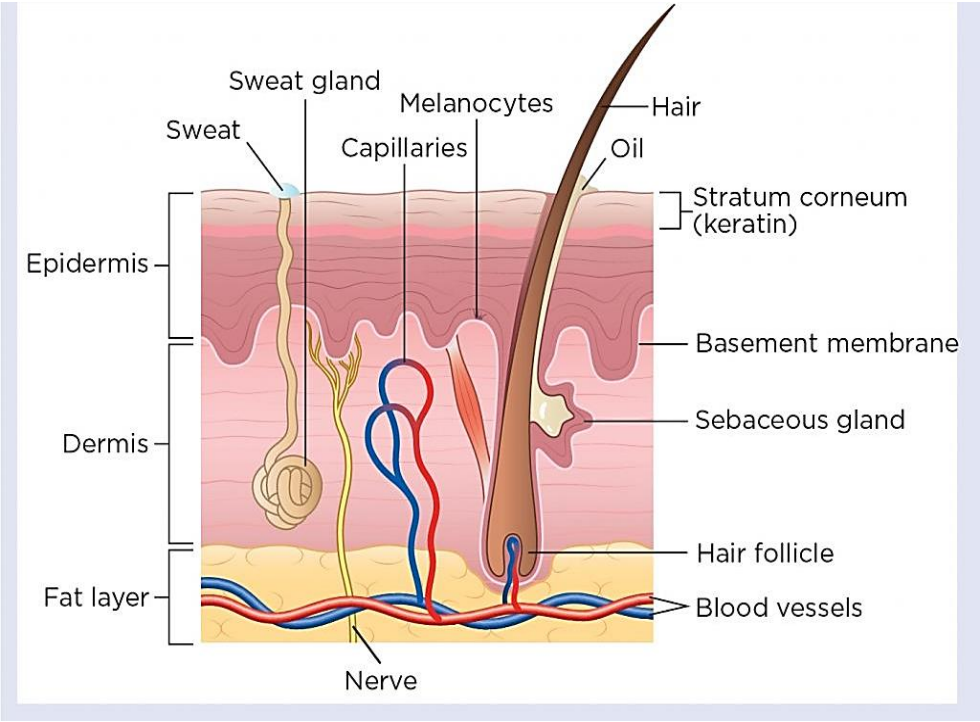

Figure 1. Cross-section through the skin.

2. 2. Keratinocytes

Keratinocytes are formed by division in the stratum basale. As they move through the stratum spinosum and stratum granulosum, differentiate to form a rigid internal structure of keratin, microfilaments and microtubules (keratinisation). The outer layer of the epidermis, the stratum corneum, is composed of layers of flattened dead corneocytes that have lost their nucleus. These cells are then shed from the skin (desquamation); this complete process takes approximately 28 days. The epidermis is made up of layers; most body parts have four layers, but those with the thickest skin have five (**Figure 2**).

The layers include:

- Stratum corneum (horny layer);
- Stratum lucidum (only found in thick skin – that is, the palms of the hands, the soles of the feet and the digits);
- Stratum granulosum (granular layer);
- Stratum spinosum (prickle cell layer);
- Stratum basale (germinative layer).

Between these corneocytes there is a complex mixture of lipids and proteins [11]; these intercellular lipids are broken down by enzymes from keratinocytes to produce a lipid mixture

of ceramides (phospholipids), fatty acids and cholesterol. These molecules are arranged in a highly organized fashion, fusing with each other and the corneocytes to form the skin's lipid barrier against water loss and penetration by allergens and irritants [12]

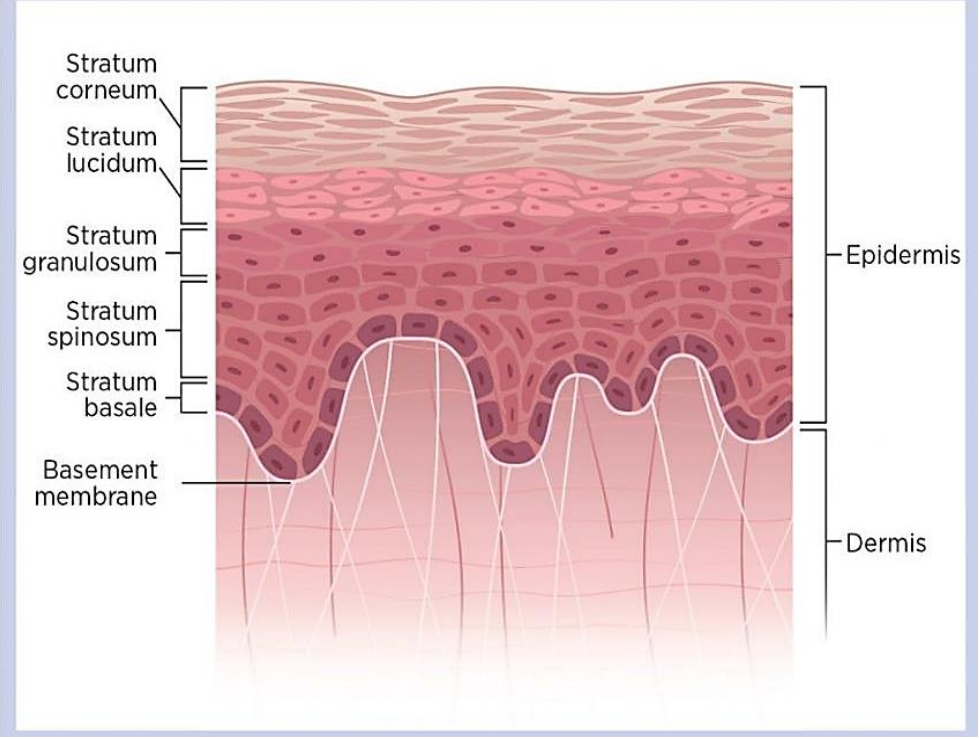

Figure 2. Layers of the Skin

2. 3. Stratum Corneum

The stratum corneum can be seen as a brick wall, with the corneocytes forming the bricks and lamellar lipids forming the mortar. As corneocytes contain a water-retaining substance and a natural moisturizing factor, they can attract and hold water. The high water content of the corneocytes causes them to swell, keeping the stratum corneum pliable and elastic, and preventing the formation of fissures and cracks [11,12]. This is important when applying topical medications to the skin which are further absorbed through the epidermal barrier into the underlying tissues and structures (percutaneous absorption) and transferred to the systemic circulation. The stratum corneum regulates the amount and rate of percutaneous absorption [13]. One of the important factors affecting this, is skin hydration and environmental humidity. In healthy skin with normal hydration, medication can only penetrate the stratum corneum by passing through the tight, relatively dry, lipid barrier between cells. When skin hydration is increased or the normal skin barrier is impaired as a result of skin disease, excoriations, erosions, fissuring or prematurity, percutaneous absorption will be increased [13].

2. 4. Melanocytes

A melanocyte is found in the stratum basale and is scattered among the keratinocytes along the basement membrane at a ratio of 1 melanocyte to 10 basal cells. Melanocytes

produces the pigment melanin that is manufactured from tyrosine, which is an amino acid, packaged into cellular vesicles called melanosomes, and transported and delivered into the cytoplasm of the keratinocytes [14]. The main function of melanin is to absorb ultraviolet (UV) radiation to protect us from its harmful effects. Skin colour is not determined by the number of melanocytes, but by the number and size of the melanosomes [10]. It is influenced by several pigments, including melanin, carotene and haemoglobin. Melanin is transferred into the keratinocytes by a melanosome. The color of the skin depends of the amount of melanin produced by melanocytes in the stratum basale and taken up by keratinocytes.

2. 5. Basement Membrane Zone (Dermo-Epidermal Junction)

This is a narrow, undulating, multi-layered structure lying between the epidermis and dermis, which supplies cohesion between the two layers [8,13].

2. 6. Dermis

Dermis forms the inner layer of the skin and is thicker than the epidermis (1-5mm) [14]. Situated between the basement membrane zone and the subcutaneous layer, the primary role of the dermis is to sustain and support the epidermis.

This network of interlacing connective tissue, which is its major component is made up of collagen and some elastin. Scattered within the dermis are several specialized cells (mast cells and fibroblasts) and structures (blood vessels, lymphatics, sweat glands and nerves).

The epidermal appendages also lie within the dermis or subcutaneous layers, but connect with the surface of the skin [13].

2. 6. 1. Layer of the Dermis

The dermis is made up of two layers namely:

- The more superficial papillary dermis;
- The deeper reticular dermis.

The papillary dermis is the thinner layer, consisting of loose connective tissue containing capillaries, elastic fibers and some collagen. The reticular dermis consists of a thicker layer of dense connective tissue which contains larger blood vessels, closely interlaced elastic fibres and thicker bundles of collagen [14]. It also contains fibroblasts, mast cells, nerve endings, lymphatics and epidermal appendages.

2. 6. 2. Specialized Dermal Cells and Structures

The fibroblast is the major cell type of the dermis and its main function is to synthesize collagen, elastin and the viscous gel within the dermis. Collagen – which gives the skin its toughness and strength – makes up 70% of the dermis and is continually broken down and replaced; elastin fibers give the skin its elasticity [10]. However, both are affected by increasing age and exposure to UV radiation, which results in sagging and stretching of the skin as the person gets older and/or is exposed to greater amounts of UV radiation [14].

Mast cells contains granules of vasoactive chemicals (the main one being histamine). They are involved in moderating immune and inflammatory responses in the skin [13]. Blood vessels in the dermis form a complex network and play an important part in thermoregulation.

2. 6. 3. Hypodermis

The hypodermis is a subcutaneous layer lying below the dermis, it largely consists of fat. It provides the main structural support for the skin, as well as insulating the body from cold and aiding shock absorption. It is interlaced with blood vessels and nerves.

2. 7. Functions of The Skin

The skin has three main functions [13].

2. 7. 1. Protection

The skin serves as a protective barrier from:

- Mechanical, thermal and other physical injury
- Harmful agents
- Excessive loss of moisture and protein
- Harmful effects of UV radiation

2. 7. 2. Thermoregulation

One of the important functions of the skin is to protect the body from cold or heat, and maintain a constant core temperature. This is done by alterations to the blood flow through the cutaneous vascular bed.

During warm periods, the vessels dilate, the skin reddens and beads of sweat form on the surface, that is, vasodilatation = more blood flow = greater direct heat loss. In cold periods, the blood vessels constrict, preventing heat from escaping, that is, vasoconstriction = less blood flow = reduced heat loss). The secretion and evaporation of sweat from the surface of the skin also helps to cool the body.

2. 7. 3. Sensation

Skin is the ‘sense-of-touch’ organ that brings about a response if we touch or feel something, including things that may cause pain. This is important for patients with a skin condition, as pain and itching can be extreme for many and cause great distress. Touch is also important for many patients who feel isolated by their skin as a result of color, disease or the perceptions of others as many experience the fact that they are seen as dirty or contagious and should not be touched.

2. 8. Biochemical Functions

The skin is also involved in several biochemical processes. In the presence of sunlight, a form of vitamin D called cholecalciferol is synthesized from a derivative of the steroid cholesterol in the skin.

The liver converts cholecalciferol to calcidiol, which is then converted to calcitriol (the active chemical form of the vitamin) in the kidneys. Vitamin D is essential for the normal absorption of calcium and phosphorous, which are required for healthy bones [15]. The skin also comprises of receptors for other steroid hormones (estrogens, progesterone and glucocorticoids) and for Vitamin A.

3. FREE RADICALS

Free radicals are defined as any molecular specie capable of independent existence that contains an unpaired electron in an atomic orbital. A free radical can contain an unpaired electron in their atomic orbital and can also exist independently. The presence of an unpaired electron can result in certain common properties that are shared by most radicals. Many radicals are very unstable and highly reactive. Free radicals are oxygen containing molecules that are highly reactive and unstable radicals are oxygen containing molecules that are highly reactive and unstable. They are formed when molecules or atoms gain or lose electrons. This results in an unpaired electron that can easily react with other molecules. Radicals can either donate an electron to or accept an electron from other molecules, therefore behaving as oxidants or reductants [16].

The important oxygen-containing free radicals in many disease states are hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical. They are highly reactive species, capable in the nucleus, and in the membranes of cells of damaging biologically relevant molecules such as DNA, proteins, carbohydrates, and lipids [17]. Free radicals can attack important macromolecules which can lead to cell damage and homeostatic disruption. Targets of free radicals can include all kinds of molecules in the body, among them are lipids, nucleic acids, and proteins.

3. 1. Properties of Free Radicals

- Free radicals are unique and rare species and are also present only under special and limited conditions.
- Nitrogen monoxide and nitrogen dioxide are also stable and free radial species. However, the reactive species which is involved in immunity are oxygen free radicals, such as super oxide anion radical and singlet molecular oxygen.
- Free radicals are very familiar to us in our lives and are also very important chemicals.
- Free radicals are very reactive and highly unstable. They can donate an electron or accept an electron from other molecules, therefore, they can behave as oxidants or reactants.

3. 2. Uses of Free Radicals

- Free radicals are present in the membranes of cells thereby, damaging biologically relevant molecules such as the DNA, lipids, proteins, and carbohydrates etc.
- The free radicals attack important macro molecules which can lead to cell damage and homeostatic disruption such as proteins, nucleic acids etc.
- Generally, alkyl halides or aryl halides are used as radical precursors. However, halogenation of sugar and nucleosides which have many OH groups and other delicate functional groups is difficult.
- Barton McCombie reaction is majorly used for the radical reactions in sugars, nucleosides and peptides.
- Other thiocarbonyl derivatives formed from alcohols with phenoxythiocarbonyl chloride, diimidazole can be used instead of methyl xanthate.

3. 3. Sources of Free Radicals

Free radicals are generated internally through the following sources: [19]

- Mitochondria
- Inflammation
- Exercise
- Phagocytosis
- Peroxisomes
- Xanthine oxidase
- Exercise
- Ischemia/reperfusion injury

Some externally generated sources of free radicals include:

- Cigarette smoke
- Environmental pollutants
- Radiation
- Certain drugs, pesticides
- Industrial solvents
- Ozone

3. 4. Production of Free Radicals in the Human Body

Free radicals are derived either from normal essential metabolic processes in human or from external sources such as exposure to X-rays, ozone, cigarette smoking, air pollutants, and industrial chemicals [20]. Free radical formation occurs incessantly in the cells as a result of both enzymatic and non-enzymatic reactions. Enzymatic reactions, which also serve as source of free radicals, include those involved in the respiratory chain, phagocytosis, in prostaglandin synthesis, and in the cytochrome P-450 system [21]. Free radicals can be formed also in non-enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions.

3. 5. Free Radical and Ageing

Research suggests that free radical damage to cells can lead to the pathological changes associated with aging. [22]. An increasing number of diseases or disorders, as aging process itself demonstrates link either directly or indirectly to these reactive and destructive molecules [23]. The major mechanism of aging applies to DNA or the accumulation of cellular and functional damage [24]. Reduction of free radicals or decreasing their rate of production might delay aging. Some of the nutritional antioxidants will slow down the aging process and prevent disease.

Based on these studies, it appears that increased oxidative stress commonly takes place during aging process, and the antioxidant status might significantly influence the effects of oxidative damage associated with advanced age. Research also suggest that free radicals have a significant influence on aging, that free radical damage can be controlled with adequate antioxidant defense, and that optimal intake of antioxidant nutrient might contribute to enhanced quality of life.

4. AGEING

Ageing is a gradual and continuous process of a natural change that begins in early adulthood. During early middle age, many bodily functions begins to gradually decline. The definition encompasses the multiple processes that the human body goes through as it ages. In addition, ageing connotes a biological and social construct [25]. Ageing is usually associated with dynamic changes in the psychological, biological, physiological, environmental, social and behavioral processes. In the broader sense, ageing refer to single cells within an organism which have ceased dividing (cellular senescence) or to the population of a species (population ageing) [26]. It can also be accumulative, such as the onset of skin damage due to excessive sun exposure.

In human beings, ageing represents the accumulation of changes in a human being over time [27] and can encompass physical, psychological, and social changes. Reaction time, for example, might slow with age, while memories and general knowledge typically increase.

Ageing increases the risk of human diseases [28] of the roughly 150,000 people who die across the globe each day, about two-thirds die from age-related causes [29].

The causes of ageing are uncertain, current theories are assigned to the damage concept, in which the accumulation of damage (such as DNA oxidation) may cause biological systems to fail, or to the programmed ageing concept, whereby problems with the internal processes (epigenomic maintenance such as DNA methylation) may cause ageing [30]. Programmed ageing should not be confused with programmed cell death (apoptosis). In addition, there can be other reasons, which can speed up the rate of ageing in organisms including human beings like obesity and compromised immune system [31].

Biologically, ageing comes from the impact of the accumulation of wide range of molecular and cellular damage over time. However, this leads to a gradual decline in physical and mental capacity, a growing risk of diseases, and ultimately death. These changes are usually consistent and are associated with a person's age in years. While some people aged 70 years might be strong and enjoy good health, others who are 70 years might be weak and require others to help them [32].

4. 1. Types of Age

4. 1. 1. Chronological age

Chronological age is based on the passage of time. It is a person's age in years. Chronological age has limited significance in terms of health. However, the likelihood of developing a health problem increases as people age. This helps predict many health problems, it has some legal and financial uses.

4. 1. 2. Biological age

Biological age refers to changes in the body that commonly occur as people age. The changes affect some people sooner than others, some people are biologically old at 65, while others might not, until a decade or more. Moreover, most noticeable differences in apparent age among people of similar chronologic age are caused by lifestyle, habit, and subtle effects of disease rather than by differences in actual aging.

4. 1. 3. Psychological age

This is based on how people act and feel. For example; an 80-year-old who plans, works, looks forward to future events, and participates in many activities is considered psychologically young.

4. 2. Types of Ageing

Digging deep into the process of ageing, there are several theories that describes how and why our bodies age on multiple levels.

4. 2. 1. Cellular Ageing

A cell can replicate like fifty times before the genetic material is no longer able to be copied accurately. The replication failure is referred to as cellular senescence in which the cell loses its functional characteristics. The accumulation of senescent cells is the hallmark of cellular ageing, which also translates to biological aging [33]. The more damage done to cells by free radicals and environmental factors, the more cells need to replicate and the more rapidly the cellular senescence develops.

4. 2. 2. Hormonal Ageing

Hormones play a big role in aging, especially during childhood when they help build bones and muscles and brings about the development of secondary male or female characteristics. As time goes on, the output of many hormones will begin to diminish, which leads to changes in the skin (such as the loss of elasticity and wrinkles) and a loss of muscle tone, sex drive and bone density.

4. 2. 3. Accumulative Damage

Ageing caused by accumulative damage ("wear and tear") is about the external factors that can build up over time. Unhealthy foods, exposure to toxins, UV radiation, and pollution can be some of the things that can take a toll on the body. Over time, these external factors can directly damage DNA in cells (by exposing them to excessive or persistent inflammation). The accumulated damage can hinder the body's ability to repair itself thereby promoting rapid ageing [34].

4. 2. 4. Metabolic Ageing

As you go about your day, the cells are constantly turning food into energy, which produces byproducts some of which can be harmful to the body. This process of metabolization, can cause progressive damage to cells, a phenomenon referred to as metabolic ageing. Some experts believe that slowing down the metabolic process through practices like calorie restriction may slow ageing in humans [35].

4. 3. How to Slow Ageing

Ageing cannot be avoided. With that said, there are several things one can do to reduce the environmental factors that influence ageing, which are:

- **Eat well:** Added sugar, salt, and saturated fat cause havoc to the body, thereby increasing the risk of hypertension, diabetes, and heart disease. To avoid these ageing-related concerns, increase your intake of fruits, vegetables, low-fat dairy, whole grains and lean meat and fish.
- **Read labels:** Before buying packaged foods, check the label to ensure that you limit your sodium intake to under 1,500 milligrams (mg) per day, your sugar intake to around 25 mg per day, and your saturated fat intake to less than 10% of your daily calories.
- **Stop smoking:** Quitting cigarettes improves circulation and blood pressure while drastically reducing the risk of cancer. Though it might take multiple quit attempts to finally kick the habit, there are effective cessation aids that can help.
- **Exercise:** Most people do not meet the recommended exercise requirements for good health (roughly 30 minutes of moderate to strenuous exercise 5 days per week). Even, 15 minutes of moderate activity per day can improve longevity compared to no exercise [36].
- **Socialize:** Socialization keeps us psychologically engaged and might help influence longevity as well. Maintain good, healthy relationships with others [37], stay connected to the ones you love, and meet new people.
- **Get ample sleep:** Chronic sleep deprivation is connected to poorer health and shorter life span [38]. By improving your sleep hygiene and getting 7 to 8 hours of sleep per night, you may not only feel better but live longer.
- **Reduce stress:** Chronic stress and anxiety can be damage the body as they trigger the release of an inflammatory stress hormone called **cortisol**. Learning to control stress with relaxation techniques and mind-body therapies may ease the indirect inflammatory pressure placed on cells [39].

4. 4. Ageing Process and Physiological Changes

4. 4. 1. Changes in nervous system

Ageing is associated with many neurological disorders, as the capacity of the brain to transmit signals and to communicate reduces. The loss of brain function is the biggest fear among elderly which can include loss of the mental functions resulting from brain tissue changes (Alzheimer's disease).

Alzheimer disease and Parkinson disease are the progressive neurodegenerative diseases associated with ageing [40]. Alzheimer's disease is characterized by progressive cognitive deterioration along with a change in behavior and a decline in the activities of daily living. Alzheimer's disease is the most common type of pre-senile and senile dementia. This disease causes nerve cell death and tissue loss all over the brain, affecting almost all its functions. The cortex in the brain shrivel up and thereby causing damage to the areas involved in planning, thinking, and remembering. The shrinkage in a nerve cell is especially severe in the hippocampus (an area of the cortex that has a key role in the formation of new memories) and the ventricles also grow larger. Alzheimer's disease causes an overall misbalance among elderly ones by causing memory loss, changes in personality and behavior-like apathy, depression, mood swings, distrust in others, social withdrawal, irritability and aggressiveness [41, 42].

4. 4. 2. Cognition

Cognitive impairments are usually observed among elderly people. Normally, these changes take place as outcomes of proximal life events, where distal events are early life

experiences like physical, cultural and social conditions that influence functioning and cognitive development [43].

Cognition decline arise from proximal factors (multiple serial cognitive processes) which includes processing speed, size of working memory, inhibition of extraneous environmental stimuli and sensory losses. This is a threat to the quality of life of those affected individuals and their caregivers [44].

Impaired cognition among elderly is associated with increased risk of injuries to self or others, the decline in functional activities of daily living and increased risk of mortality [45-47]. Mild cognitive impairment is increasingly recognized as a transitional state between normal ageing and dementia [48, 49].

4. 5. Special Senses

- **Vision**: Ageing include a decline in accommodation (presbyopia), glare tolerance, adaptation, low-contrast activity, attentional visual fields and color discrimination. Changes takes place in the central processing and in the components of the eye. These numerous changes affect reading, balancing and driving [50].
- **Hearing**: Ageing causes conductive and sensory hearing loss (presbycusis); the loss is primarily high tones, making consonants in speech difficult to discriminate. [51]
- **Taste acuity**: Losing sense of taste is a common problem among the elderly [52]. Taste acuity does not reduce but salt detection declines. The salivary gland gets affected, and the volume and quality of saliva diminish. All changes combine to make eating less interesting [53]. Studies has shown that the physiological decline in the density of the taste acuity and papillae results in a decline of gustatory function [54]. In fact, studies done on taste dysfunction show that ageing-associated changes in the density of taste acuity may affect taste function differently in different regions of the tongue [55]. Taste perception declines during the normal ageing process. A study done on the healthy elderly shows that after about 70 years of age, taste threshold begins to increase resulting in dysgeusia [55]. Chewing problems associated with loss of teeth and use of dentures also interfere with taste sensation and cause reduction in saliva production [53].
- **Smell:** As we get older, our olfactory function declines [56]. Hyposmia (reduced ability to smell and to detect odors) is also observed with normal ageing [57]. The sense of smell reduces as the age increases, and this affects the ability to discriminate between smells. A decreased sense of smell can lead to significant impairment of the quality of life, including taste disturbance and loss of pleasure from eating with resulting changes in weight and digestion. It has been reported that more than 75% of people over the age of 80 years have evidence of major olfactory impairment. Many long-term studies show the evidence of a decline in olfaction considerably after the seventh decade [58]. Another study found that 62.5% of 80–97-year-olds had olfactory impairments [59]. However, it is widely accepted that taste disorders are far less prevalent than olfactory losses with age. Ageing also causes atrophy of olfactory bulb neurons. Central processing is therefore altered, resulting in a decreased perception and less interest in food [60].
- **Touch:** As we age, our sense of touch often declines due to skin changes and reduced blood circulation to touch receptors or to the brain and spinal cord. Minor dietary deficiencies such as the deficiency of thiamine may also be a cause of changes [61]. The sense of touch also includes awareness of vibrations and pain. The skin, muscles, tendons, joints and internal

organs have receptors that detect touch, temperature or pain [62]. A decline in the sense of touch affects simple motor skills, hand grip strength and balance. Studies have shown that muscle spindle (sensory receptors within the muscle that primarily detects changes in the length of this muscle) and mechanoreceptor (a sense organ or a cell that responds to mechanical stimuli such as touch or sound) functions decline with ageing, further interfering with balance [63].

4. 6. Effects of Ageing

A number of characteristic ageing symptoms are experienced by a majority or by a significant proportion of humans during their lifetimes.

- Teenagers lose the young child's ability to hear high-frequency sounds above 20 kHz [64].
- Wrinkles start to develop mainly due to photo--aging, particularly affecting sun-exposed areas (face) [65].
- After peaking in the mid-20s, female fertility declines.
- After age 30 the mass of human body decreases until 70 years and then shows damping oscillations. [66]
- Muscles have reduced capacity of responding to exercise or injury and loss of muscle mass and strength (sarcopenia) is common [67]. Maximum oxygen utilization and maximum heart rate decline [68].
- Hand strength and mobility decreases during the ageing process. These things include, "hand and finger strength and ability to control submaximal pinch force and maintain a steady precision pinch posture, manual speed, and hand sensation" [69]
- People over 35 years of age are at increasing risk for losing strength in the ciliary muscle of the eyes which leads to difficulty focusing on close objects, or presbyopia [70]. Most people experience presbyopia by age 45–50 [71]. The cause is lens hardening by decreasing levels of alpha-crystallin, a process which may be sped up by higher temperatures. [72]
- Around age 50, hair turns grey [73]. Pattern hair loss by the age of 50 affects about 30–50% of males [74] and a quarter of females [75].
- Menopause typically occurs between 44 and 58 years of age [76].
- In the 60–64 age cohort, the incidence of osteoarthritis rises to 53%. Only 20% however report disabling osteoarthritis at this age [77].
- Almost half of people older than 75 have hearing loss (presbycusis) inhibiting spoken communication. Many vertebrates such as fish, birds and amphibians do not suffer presbycusis in old age as they are able to regenerate their cochlear sensory cells, whereas mammals including humans have genetically lost this ability. [78]
- By age 80, more than half of all Americans either have a cataract or have had cataract surgery.
- Frailty, a syndrome of decreased strength, physical activity, physical performance and energy, affects 25% of those over 85 [79].
- Atherosclerosis is classified as an ageing disease [80]. It leads to cardiovascular disease (for example stroke and heart attack) [81] which globally is the most common cause of death. Vessel ageing causes vascular remodeling and loss of arterial elasticity and as a result causes the stiffness of the vasculature.

- Recent evidence has suggested that age-related risk of death plateaus after age 105. The maximum human lifespan is suggested to be 115 years [82,83]. The oldest reliably recorded human was Jeanne Calment who died in 1997 at 122.

5. THEORY OF FREE RADICALS

Free radicals are unstable atoms which can damage cells, cause illness and aging.

- Atoms are surrounded by electrons that orbit the atom in layers called shells. Each shell needs to be filled by a set number of electrons. When a shell is full, electrons begin filling the next shell.
- If an atom has an outer shell that is not full, it might bond with another atom, using the electron to complete its outermost shell. These types of atoms are known as free radicals.

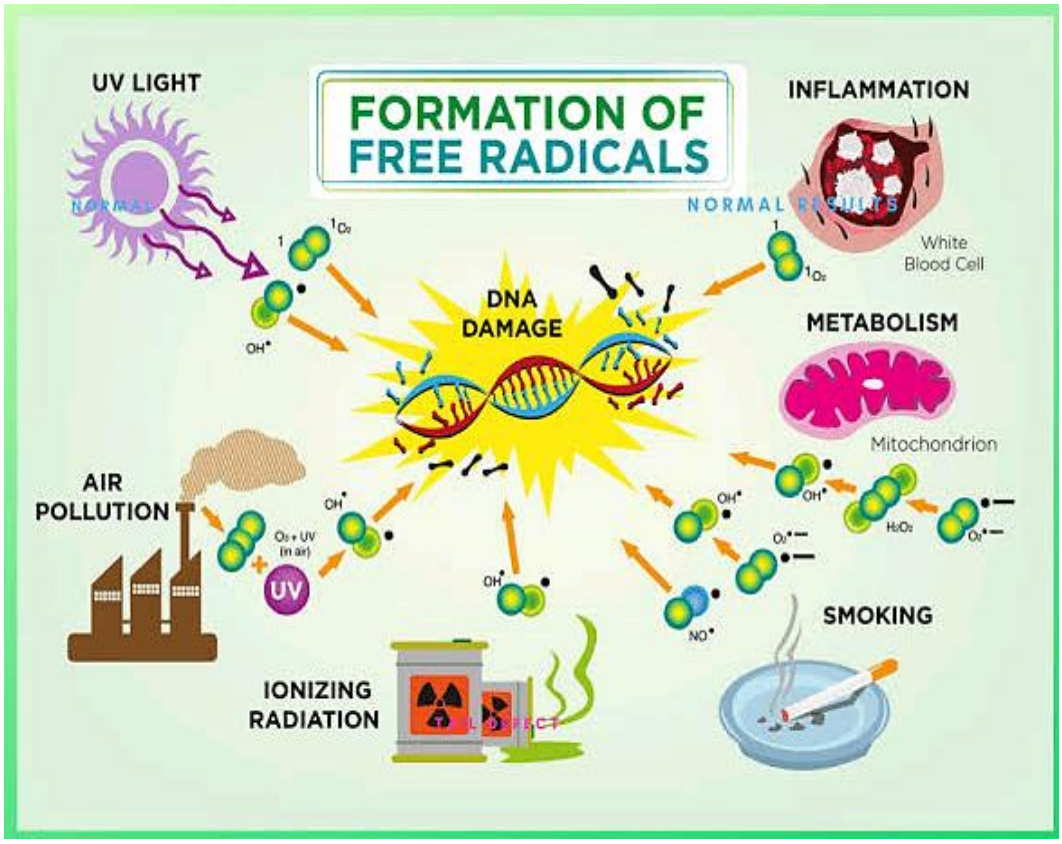

Figure 3. Free radicals causing DNA damage

The reactivity of free radicals is what poses a threat to macromolecules like DNA, RNA, proteins, and fatty acids. Free radicals can cause chain reactions that ultimately damage cells. For example;

- A superoxide molecule might react with a fatty acid and take one of its electrons. The fatty acid then becomes a free radical that can react with another fatty acid nearby. As this chain

reaction continues, the permeability and fluidity of cell membranes changes, proteins in cell membranes experience decreased activity, and receptor proteins undergo changes in structure that either alter or stop their function. If receptor proteins designed to react to insulin levels undergo a structural change it can negatively affect glucose uptake. Free radical reactions can continue unchecked unless being stopped by a defense mechanism.

5. 1. The Body's Defense

Free radical development is unavoidable, but human bodies have adapted by maintaining and setting up defense mechanisms that reduce their impact. The body's two major defense systems are antioxidant chemicals and free radical detoxifying enzymes.

- An antioxidant is any molecule that can block free radicals from stealing electrons; antioxidants act both inside and outside of cells.
- Free radical detoxifying enzyme systems are responsible for protecting the inside of the cell from free radical damage.

5. 2. The Body's Offense

While our bodies have acquired multiple defenses against free radicals, we also use free radicals to support its functions. For example,

- The immune system uses the cell-damaging properties of free radicals to kill pathogens. First, immune cells engulf an invader (such as a bacterium), then they expose it to free radicals such as hydrogen peroxide, which destroys its membrane. The invader is thus neutralized.
- Scientific studies also suggest hydrogen peroxide acts as a signaling molecule that calls immune cells to injury sites, meaning free radicals may aid with tissue repair when you get cut.
- Free radicals are necessary for many other bodily functions as well. The thyroid gland synthesizes its own hydrogen peroxide, which is required for the production of thyroid hormone. Reactive oxygen species and reactive nitrogen species, which are free radicals containing nitrogen, have been found to interact with proteins in cells to produce signaling molecules. The free radical nitric oxide has been found to help dilate blood vessels and act as a chemical messenger in the brain.
- By acting as signaling molecules, free radicals are involved in the control of their own synthesis, stress responses, regulation of cell growth and death, and metabolism.

5. 3. Oxidative Stress and Antioxidants

Oxidative stress is caused when there's an imbalance between free radicals and antioxidants. Oxidative stress means that free radicals are triggering chain reactions in the body where lipids, proteins and DNA are being altered. These alterations can increase the risk for a number of disease.

Antioxidants are substances that slows down cell damage caused by free radicals. Studies have shown that diets full of plant powered antioxidant foods like fruits, vegetables, legumes and whole grains might reduce the risk of chronic disease often associated with oxidative stress. They also help to strengthen the immune system, which fights harmful infections.

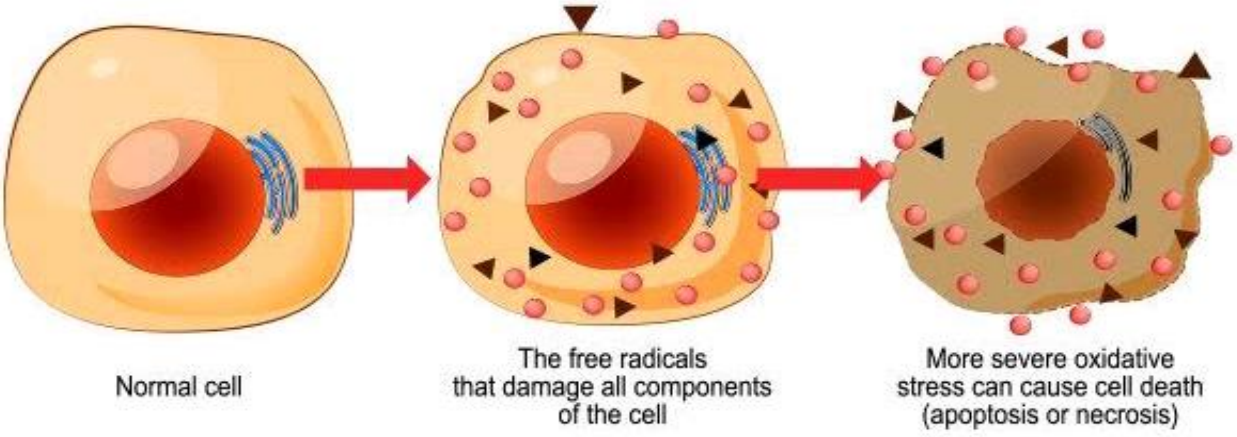

Figure 4. Induction of Oxidative Stress

5. 4. Theory of Ageing

Modern biological theories of ageing in humans is currently divided into two main categories:

- Programmed theories
- Damage or error theories.

The programmed theories imply that ageing follows a biological timetable (regulated by changes in the gene expression that affect the systems responsible for maintenance, repair and defense responses), while the damage or error theories emphasize environmental assaults to living organisms that induce cumulative damage at various levels as the cause of ageing [84].

These two categories of theory [85] are also referred to as non-programmed aging theories based on evolutionary concepts (where ageing is considered the result of an organism's inability to better combat natural deteriorative processes), and programmed ageing theories (which consider ageing to ultimately be the result of a biological mechanism or program that purposely causes or allows deterioration and death in order to obtain a direct evolutionary benefit achieved by limiting lifespan beyond a species-specific optimum lifespan.

There are three sub-categories of the programmed theory, and four sub-categories of the damage or error theory, and also relates some to how these might be observed in ageing populations. [84]

5. 4. 1. The Programmed Theory

- **Programmed Longevity:** this considers ageing to be the result of a sequential switching on and off of certain genes, with senescence being defined as the time when age-associated deficits are manifested.
- **Endocrine Theory:** where biological clocks act through hormones to control the pace of ageing.
- **Immunological Theory:** This theory states that the immune system is programmed to decline over time, leading to an increased vulnerability to infectious disease and thus ageing and death.

5. 4. 2. The Damage or Error Theory

- **Wear and tear theory:** where vital parts in our cells and tissues wear out resulting in ageing.
- **Rate of living theory:** this supports the theory that the greater an organism's rate of oxygen basal, metabolism, the shorter its life span
- **Cross-linking theory:** according to which an accumulation of cross-linked proteins damages cells and tissues, slowing down bodily processes and thus result in ageing.
- **Free radical's theory:** which proposes that superoxide and other free radicals causes damage to the macromolecular components of the cell, which gives rise to accumulated damage causing cells, and eventually organs, to stop functioning.

5. 5. Types of Ageing Theory

5. 5. 1. The Disengagement Theory

This theory refers to an inevitable process in which many of the relationships between a person and other member of a society are severed & those remaining are altered in quality. Withdrawal may be initiated by the ageing person or by society, and may be partial or total. It was observed that older people are less involved with life than they were as younger adults. As people age they experience greater distance from society and they develop new types of relationships with society. Some suggest that this theory does not consider the large number of older people who do not withdraw from society. The disengagement theory is also recognized as the first formal theory that attempted to explain the process of growing older [86].

5. 5. 2. The Activity Theory

Activity theory describes the psychosocial ageing process. It emphasizes the importance of ongoing social activity. This theory suggests that a person's self-concept is related to the roles held by that person, that is, retiring may not be so harmful if the person actively maintains other roles, such as familial roles, recreational roles, volunteer & community roles. To maintain a positive sense of self the person must substitute new roles for those that are lost because of age [87].

5. 5. 3. The Neuroendocrine Theory

This theory was first proposed by Professor Vladimir Dilman and Ward Dean, the neuroendocrine theory elaborates on wear and tear by focusing on the neuroendocrine system. This system is a complicated network of biochemical that governs the release of hormones which are altered by the walnut sized gland called the hypothalamus which is located in the brain. The hypothalamus controls various chain-reactions to instruct other organs and glands to release their hormones etc.

The hypothalamus also responds to the body hormone levels as a guide to the overall hormonal activity. But as we grow older the hypothalamus loses it precision regulatory ability and the receptors which uptake individual hormones become less sensitive to them. Consequently, as we age the secretion of many hormones declines and their effectiveness (compared unit to unit) is also reduced due to the receptors down-grading [88, 89].

5. 5. 4. The Free Radical Theory

This very famous theory of ageing was developed [90] by Denham Harman at the University of Nebraska in 1956. The term free radical describes any molecule that has a free electron, and this property makes it react with healthy molecules in a destructive way. Because the free radical molecule has an extra electron it creates an extra negative charge. This unbalanced energy makes the free radical bind itself to another balanced molecule as it tries to steal electrons.

By do that, the balanced molecule becomes unbalanced and thus a free radical itself. It is known that diet, lifestyle, drugs (e.g. tobacco and alcohol) and radiation etc., are all accelerators of free radical production within the body [88]. There are numerous studies that demonstrate that ROS and oxidative damage increase with age [92] and that reducing oxidative damage extends the lifespan of various model organisms (yeast, nematodes, fruit flies, mice, etc.), as well as that increased production of ROS shortens lifespan [93].

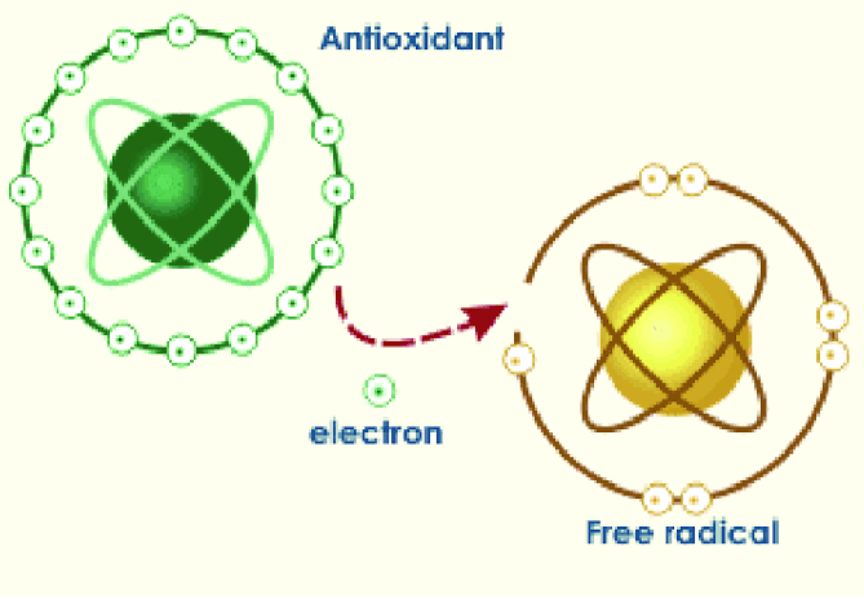

Figure 5. Role of Antioxidant in neutralizing free radical

Domination of the free radical theory has been little affected by an increasing number of studies that seem to contradict it. For example, although in some experimental systems, antioxidant proteins extend lifespan, their overexpression in other systems was found to be ineffective [94]. These findings also hold when the system is controlled for appropriate regulation and expression levels of these proteins [95]. Increased antioxidant protection may even lead to shortened lifespan, whereas decreased antioxidant function may extend it [96]. Evidence against the idea of the universal role of ROS in the aging process also includes the observation that aging still occurs under anaerobic conditions, where there is little ROS. Specifically, the lifespan of anaerobically grown yeast cells is shorter compared with the cells grown aerobically (rather than longer as would be expected if ROS are the cause of aging), not regulated by antioxidant enzymes (whereas these enzymes may regulate it under aerobic

conditions), and is further shortened (rather than extended as commonly observed for this dietary regimen) by caloric restriction [97].

To reconcile the free radical theory with the observations that contradict it, researchers have proposed that ROS may serve signaling functions, thereby activating protective and adaptive programs [98,99]. It was also proposed that it is necessary to consider positional effects of ROS generation and primary targets of these reactive species [100]. Indeed, if oxidative stress occurs in localized areas of the cell, analyses of total oxidative damage may not represent the actual damage inflicted by ROS. Whereas these arguments help address many experimental contradictions, many other questions remain. For instance, these arguments do not explain the fact that the utilization of molecular oxygen, the precursor for ROS, is not universally required for the aging process. However, these arguments may not even be necessary, if oxidative damage is viewed in the context of a model that considers aging as a product of biological imperfectness leading to inevitable accumulation of the myriad damage forms.

5. 6. Biological Imperfectness and the Ageing Process

Biomolecules and biological processes are imperfect, manifesting in unintended activities and functions. Thus, damage, in the form of by-products, errors of all sorts, misbalance in cellular components, etc., is produced by each and every cellular process [100, 101]. For example, consider enzymes. They have impressive specificity, but they are not perfect and generate minor reaction products and other unwanted by-products [102, 103].

Enzymes' fidelity is restricted by the fact that they are flexible polymers that exist in various conformations and are made of a limited set of amino acids and cofactors. It is further compromised by errors in protein sequence and structure resulting from errors in transcription, translation, folding, and post-translational modifications, by mutations and genetic variability, and by other factors. In other words, not a single enzyme is perfect, no matter how well its active site is built by the combined action of its amino acid residues and cofactors. Besides making the main product from its substrate through its direct (evolved) function, the enzyme produces a little bit of something else and occasionally reacts with molecules other than its natural substrate, which are the manifestations of its indirect (not evolved) functions. It should be noted that such by-products are largely not random. They are governed by catalytic properties of each enzyme; their chemical identity and rates of accumulation can be changed during evolution. Thus, a gene encoding an enzyme codes for both direct and indirect functions of this enzyme, both of which are genetically controlled.

However, the enzyme-generated by-products only account for a fraction of the damage produced in cells because all other cellular components and systems are also imperfect and heterogeneous. It may be expected that each cellular reaction and all macromolecular interactions generate damage through indirect functions of biomolecules. More broadly, damage will necessarily arise from imperfectness, heterogeneity, and noise of biological systems. Similarly, variability in gene and protein expression will result in cell-to-cell differences as well as differences among individual organisms of the same species. Many minor products of cellular metabolism are simply not detectable because methods do not exist that can analyze them, or because an averaged signal is analyzed. The concept of by-products of catalytic reactions is well accepted in chemistry, but biologists tend to operate in terms of perfect biological systems, overlooking this fundamental principle. Biology increases complexity, but nothing disappears from chemistry when it comes to biology.

Cellular damage generated as a result of imperfectness would certainly include oxidative damage. However, the latter, like any other damage form, would only represent a subset of total damage, which, regardless of its contribution to the regulation of lifespan, would have nothing to do with the cause of aging [100, 101]. How does the cell deal with the damage? Much of the damage remains confined within the space surrounded by cellular and organelle membranes. Many cellular by-products that represent more severe damage and immediate danger can be cleared up by the protection and repair systems that metabolize or export damage from the cell.

There are also related strategies, such as the so-called Maxwell's demons, which represent the processes that by generating the progeny from within the old (e.g., budding process in yeast) result in an unequal distribution of molecular damage between cells [104]. However, irrespective of the specific strategies that help clear and redistribute the damage, the number of damage forms would always be greater than the number of protective systems. This is because each biological process generates damage and because clearance systems, while removing certain damage types, generate other damage types. Therefore, the damage will inevitably accumulate in the cell unless the cell divides, diluting its damage. Sooner or later, depending on the regulation imposed by natural selection, damage accumulating in post mitotic cells will compromise cellular function and the cell will senesce and die. Non-dividing cells can modulate the time to senescence by altering their metabolism and by the selective use of designated protective systems, but cannot completely stop the process of damage accumulation, and therefore cannot avoid cell death.

As oxidative damage represents only a subset of total damage, its behavior and impact on cellular function will characterize cumulative damage under some conditions, but not under other conditions. Therefore, oxidative damage and the associated clearance systems may regulate lifespan, or they may not, depending on the contribution of oxidative damage to the overall damage. We may expect much variability in the role of oxidative damage in aging among different cell types, genotypes, metabolic states (e.g., depending on the use of molecular oxygen), various species, and different environmental conditions. These considerations obviate the need to consider localized Reactive Oxygen Species (ROS) or a balance between generation and removal of oxidative damage as well as contradictory data on the role of ROS and their clearance in regulating lifespan. ROS may simply be irrelevant to aging under certain conditions, such as anaerobic growth, but may be relevant under other conditions, such as hypoxia. As such, the ROS contribution will be greatly influenced by other processes and will be dependent on numerous other factors that regulate cellular life. More importantly, neither ROS nor any other damage forms would represent the actual cause of aging, since the underlying reason the damage is generated, and cannot be fully cleared, is biological imperfectness.

6. SUMMARY AND CONCLUSION

Skin ageing is an inevitable biological phenomenon of human life that results from either the age-dependent decline of cell function (intrinsic ageing) or from cumulative exposure to external harmful influences (extrinsic ageing). Intrinsic and extrinsic factors act synergistically to induce skin changes that manifest clinically as burns, erythema, hyperpigmentation, telangiectasia, skin dryness or sagging, coarse wrinkles, skin texture changes or eventually as skin cancer. The molecular mechanisms of both types of skin aging are similar. This review

focuses on intrinsic and extrinsic mechanisms of skin aging, and on current and new perspectives for prevention and treatment options extracted from natural products.

Cutaneous ageing is the result of genetically determined or intrinsic aging superimposed by degenerative changes due to actinic irradiation, also called photo-ageing. The manifestations of cutaneous aging, as it relates to the perception of age, is caused by ultraviolet light, in particular in those parts of the body exposed daily to solar radiation. Free radical generation in the skin by UV light and from other sources, such as cellular infiltrations or the xanthine oxidase reaction, may be detected by direct and indirect methods. The decrease in antioxidant enzymes and small molecular weight antioxidants such as glutathione, vitamin E and ubiquinone upon exposure to UV light is an indication that the pro-antioxidant balance can be overwhelmed by chronic or acute photo-oxidative stress. Antioxidant supplementation is also a means for prevention or at least retardation of premature cutaneous ageing.

Biography

Babatunde Oluwafemi Adetuyi currently works at the Biochemistry unit, Department of Natural Sciences Precious Cornerstone University. His current area of research focus on Chemoprevention and Oxidoinflammation in different organs (Brain, liver, kidney, testis) using rat and mouse models as well tissue culture technique. His research technique involves PCR, Immunofluorescence, Immunohistochemistry, ELISA, and analysis, tissue preparation for histology.

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