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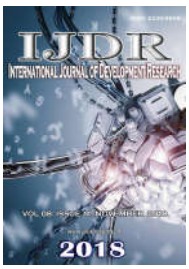

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

A SYSTEMATIC REVIEW OF AGING AND ITS CAUSES

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ABSTRACT

Aging is the accumulation of detriment which may lead to decline in normal function on cellular, tissue and organ level that ultimately causes age-related diseases and death over time. Genetics, intrinsic (endogenous) and extrinsic (environmental) factors play potential role in complex process of aging. Aged skin shows abnormalities in angiogenesis, immune system, vitamin D synthesis, wound healing and sweat and lipid production causing benign and malignant cancers. The ongoing overview uncovers the relationship between intrinsic and extrinsic skin aging processes. The effect of shortening of telomeres during every cell division is also a factor to determine skin aging. Natural products have been the essential source of medicines since ages. The purpose of skin anti-aging is to slow, cease or reverses the process of aging just to expand the life span of skin of individual. Many natural products from plant extracts and animal by-products have been employed as anti-aging agents in commercially available products.

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INTRODUCTION

Aging is the accumulation of detriment which may lead to decline in normal function on cellular, tissue or organ level that ultimately causes age-related diseases and death over time (Gkogkolou and Böhm, 2012). Many diseases involved in aging, including diabetes, atherosclerosis, osteoporosis and rheumatoid arthritis, are caused by pathophysiology of free radical formation, dysfunction of innate and adaptive immunity and DNA repair process (Dunn and Koo, 2013). Genetics, endogenous (intrinsic) and environmental (extrinsic) factors play major role in complex process of aging (Vierkötter and Krutmann, 2012; Viña *et al.,* 2007). The complex natural process of skin aging is impacted by intrinsic (genetics, metabolic pathways and hormones) and extrinsic (chronic UV radiation exposure, pollution, cigarette smoke, chemicals, toxins) factors (Bernhard *et al.,* 2007; Ganceviciene *et al.,* 2012). The largest organ of human body is skin that acts as a boundary between environment and organism. Skin is exposed to internal and external aging processes that leads to changes in physiological functions and appearance of skin.

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Aged skin shows abnormalities in angiogenesis, permeability, sweat and lipid production, immune system, vitamin D synthesis and abnormal wound healing, atrophy and cause benign and malignant disorders (Gkogkolou and Böhm, 2012; Zouboulis and Makrantonaki, 2011).

Intrinsic Skin Aging: The intrinsic skin aging is described by functional changes rather than by morphological changes. Clinical symptoms are rough and pale skin with fine wrinkles, loss of hair growth, sweating problem and a variety of benign neoplasms (Halder and Ara, 2003; Sjerobabski-Masnec and Situm, 2010; Tschachler and Morizot, 2006). The intrinsic skin aging is also affected by hormonal changes which arise with age (Makrantonaki *et al.,* 2006) like declined biosynthesis of sex hormones and attenuation of estrogens and progesterone related with menupause. It has been determined that degradation of collagen, dryness, reduction in elasticity, atrophy of epidermis and wrinkling are associated with low levels of estrogen and androgens (Ohnemus *et al.,* 2006). Reactive oxygen species (ROS) have major role in skin aging. About 1.5-5% of oxygen utilized in skin is transferred into ROS by intrinsicpathways (Poljšak *et al.,* 2012). ROS are generated in aerobic respiration as a side product (Farage *et al.,* 2008). ROS promote the transcriptional factor c-Jun by mitogen activated protein kinases (MAPK) and result in up

regulation of matrix metalloproteinase (MMP-1), MMP-3 and MMP-9 thus hinder the procollagen-1 to express (Kohl *et al.,* 2011). High levels of disrupted collagen and low biosynthesis of collagen leads to aged skin (Papakonstantinou *et al.,* 2012). Skin has a wide variety of antioxidants that are categorized as enzymatic anti-oxidants including Glutathione peroxidase, Superoxide dismutase, catalase and non-enzymatic anti-oxidants including Glutathione (GSH), ubiquinol, Vitamin C, Vitamin E and uric acid (Poljšak *et al.,* 2012). Manganese Superoxide Dismutase (MnSOD) is an enzyme that neutralizes these ROS that are produced continuously (St Clair and Kasarskis, 2003). Skin moisture is also main factor to cause skin aging. The molecule which is responsible to maintain skin moisture is Hyaluronan or Hyaluronic acid (HA) which is a glucosaminoglycan (GAG) having remarkable ability to bind and hold water molecule (Baumann L, 2007). HA is located in dermis and epidermis of skin having basic role in hydration and lubrication of joints (Burdick and Prestwich, 2011). The gene that is coded for HA is Hyaluronic acid synthase (HAS) which is regulated by transforming growth factor (TGF-β1) in skin (Stern and Maibach, 2008). Level of HA falls in epidermis while remains almost the same in dermis in aged skin. The reason for this change is still unclear (Papakonstantinou *et al.,* 2012).

Extrinsic Skin Aging: Extrinsic skin aging is described by morphological and physiological changes which ultimately cause premature skin aging. The clinical symptoms are coarse wrinkles, pigment irregularities and solar elastosis with stiffened, twisted and shapeless elastic structures having particles of elastin and collagen. The mean thickness of epidermis reduces with age in either intrinsic or extrinsic skin aging process. The extent of skin aging caused by extrinsic factors depends on exposure of individual to environmental agents(Halder and Ara, 2003; Mehta and Fitzpatrick, 2007; Sjerobabski-Masnec and Situm, 2010; Tschachler and Morizot, 2006). The major factor of extrinsic skin aging is contact to UV radiation which is categorized as photo aging. The rate of degeneracy of skin is dependent on duration, frequency and intensity of exposure to sun light (Kammeyer and Luiten, 2015). UV radiations are responsible to cause 80% of skin aging (Friedman *et al.,* 2016). Photo aged skin has less elasticity, dilated superficial blood vessels, dry and rough texture, wrinkles and pigmentation. Changes at tissue level include thick epidermis, abnormal keratinocytes, less collagen in dermal layer and atypical elastin (dermal elastosis) (Green *et al.,* 2011; Hughes *et al.,* 2013). The major source of UV radiations is sun light. UV-C radiations having wavelength 100-290 nm, completely absorbed by ozone thus have no effect on skin. UV-B radiations having wavelength 290-320 nm, cause sunburns by affecting the epidermis of skin. UV-A radiations, having wavelength of 320-400 nm, have ability to enter deep in skin and have more damaging effects on skin (Halliwell and Gutteridge, 2015; Pandel *et al.,* 2013).

Anti-Aging Agents from Natural Sources: Natural products have been the essential source of medicines commercially. This section will summarize some natural product extracts that are used as anti-aging agents.

Role of Telomeres in Aging: Telomeres are DNA-protein regions which are present at both ends of chromosomes and are responsible for stabilizing the integrity of chromosomes by saving them from unwanted recombination, end-to-end fusion and nucleolytic degradation.

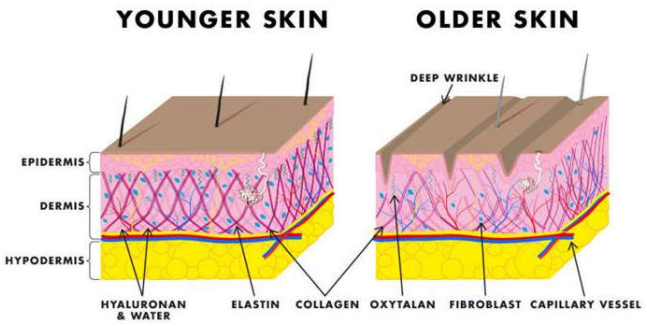

Figure 1. Diagram showing difference between young and aged skin

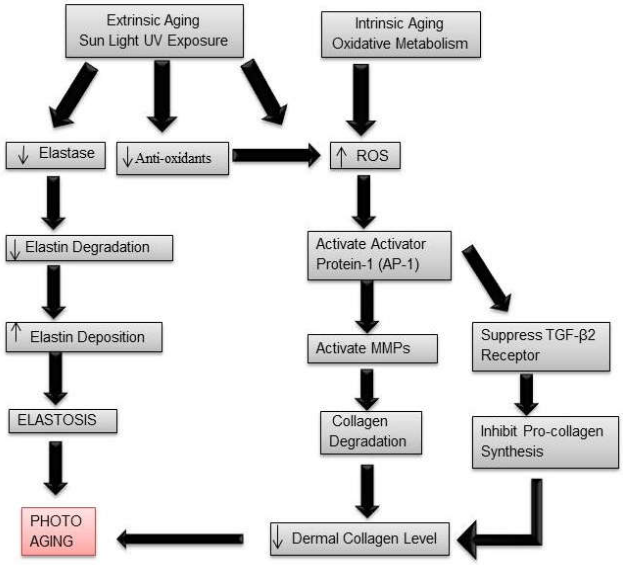

Figure 2. Figure showing relationship between Intrinsic and Extrinsic Skin Aging Processes (Mehta and Fitzpatrick, 2007) Modified.

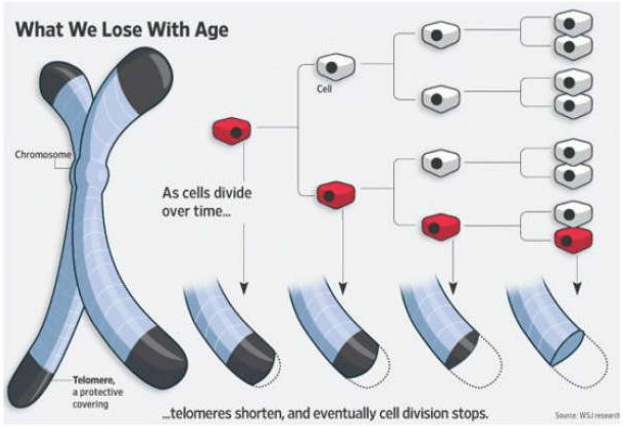

Figure 3. Diagram showing the shortening of telomeres after every cell division.

Telomeres are non-coding regions having guanine rich tandem repeats (TTAGGG) which expand 9-15 Kb in *Homo sapiens*(Houben *et al.,* 2008; Palm and de Lange, 2008; Shammas, 2011; Zhu *et al.,* 2011). The telomeric length shortens during every cell division (about 50-200 bp region is lost every cell division). As the lagging strand is not replicated properly during DNA replication, DNA polymerase cannot synthesize it completely and this is referred as end-replication problem.

Table 1. Summary of anti-aging agents from natural sources

Sr. No.	Agent	Nature	Source	Role in Anti-Aging
i.	Resveratrol	Polyphenol	Grapes, Berries and Peanuts	Anti-oxidant Anti-aging
ii.	Chlorogenic Acid	Polyphenol	Coffee and Tea	Anti-oxidant
iii.	Gallic Acid	Polyphenol	Higher Plants	Anti-oxidant
iv.	Hesperidine	Flavonoid	Citrus Fruits	Anti-oxidant Anti-inflammatory
v.	Oligonol	Polyphenol	Lychee Extract	Anti-oxidant Anti-cancer Anti-inflammatory
vi.	Urolithin A	Benzo-coumarins	Pomegranate, Nuts and Berries	Anti-aging Reduces ROS species
vii.	Lutein	Carotenoid	Green Vegetables and Eggs	Anti-oxidant Anti-senescent activity
viii.	Theaflavin	Polyphenol	Black Tea	Anti-oxidant Anti-cancer Anti-inflammatory
ix.	Fisetin	Flavonoid	Strawberries	Anti-oxidant Anti-cancer Anti-inflammatory
x.	Tyrosol	Polyphenol	Olive Mill Waste	Anti-oxidant Anti-inflammatory Antimicrobial

Table 2. Approaches for Skin Anti-aging

Classification	Procedure
Cosmetics	Skin Care
(Non-Invasive Procedure)	Sun Protection
Topical Agents	Antioxidants
Invasive Procedure	Chemical peels
	Injectable Skin Rejuvenation and Dermal fillers Platelet-Rich Plasma (PRP)
Systemic Procedures	Hormone Replacement Therapy (HRT)

When the chromosomal length reaches a point where it become difficult to survive, the cell undergoes apoptosis (Fyhrquist and Saijonmaa, 2012; Muraki *et al.,* 2012; Orren, 2006). The shortening of telomeric ends serves as mitotic clock to avoid uncontrolled cell division and hence cancer. This protective mechanism results in cell senescence and is an indicator for aging. The length of telomere is not only the factor which determines the fate of cell but the presence of telomerase is also important. The active telomerase helps to sustain the length of telomere in germ line and cancer cells. The activity of telomerase has also been seen in the somatic cells of epidermis but this enzyme is unidentified in dermis. In human, telomerase subunit that acts as template is telomerase RNA component (TERC) while Telomerase Reverse Transcriptase (TERT) serves as catalytic subunit. These two subunits are required to synthesize the telomeric DNA ends (Buckingham and Klingelhutz, 2011; Cohen *et al.,* 2007; Gragnani *et al.,* 2014; Zhu *et al.,* 2011).

Other factors causing skin aging

Smoking: Tobacco smoking is a major cause of morbidity and directly related to lung cancer, cardiovascular disorders, bronchitis and other cancers (Morita, 2007). Tobacco smoking starts numerous dermatological conditions including squamous cell carcinoma, premature skin aging, melanoma, delayed wound healing, oral malignancy, psoriasis, acne, dermatitis, and alopecia. Tobacco smoking is responsible for harmful impacts on skin epidermis directly and on the dermis indirectly through blood stream. The diminished moisture present in the stratum corneum of the skin of face adds to facial wrinkling because of direct exposure to the smoke. Pressing together the lips amid smoking with constriction of the muscles of face and squinting because of eye disturbance from the smoke can cause the development of wrinkles around the eyes and mouth (crow's feet). Molecular alterations in the dermis incorporate low collagen formation, MMP activation, over accumulation of elastic fibers (Mackiewicz and Rimkevicius, 2008; Morita 2007, 2016).

Air Pollution: Air pollution is another environmental factor to cause skin aging. Unwanted effects of air pollutants or contaminants on human wellbeing are of major concern and have been appeared to incorporate risk for cancer, cardiovascular diseases and respiratory disorders (Beelen *et al.,* 2008; Castaño-Vinyals *et al.,* 2008). The skin is the organ which as peripheral barrier is in continuous contact with different air toxins, therefore the relationship between air pollution and skin destroying effects causing skin aging. It has been reported that ozone, as a solid oxidative agent, influences the integrity of the skin. Furthermore, ozone could instigate the expression of MMP-9 in murine skin demonstrating a role in matrix remodeling (Valacchi *et al.,* 2003). A recent study showed direct connection between exposure to airborne particulate matter (PM) and skin aging signs particularly pigmentation or wrinkles formation (Vierkötter *et al.,* 2010). PM shows its harmful effects by production of ROS (Donaldson *et al.,* 2005). To prevent adverse effects of air pollution, no proper therapies or cosmetic products are available yet.

Skin Anti-Aging: The purpose of skin anti-aging is to slow, cease or reverses the process of aging just to expand the life span of skin of individual (Binstock, 2004). Various therapies have been introduced for prevention of skin aging including skin care by using anti-aging creams, sun blocks to prevent direct sun light exposure, antioxidants, invasive procedures, chemical peels, Hormone Replacement Therapy (HRT) and Platelet-Rich Plasma (PRP)(Ganceviciene *et al.,* 2012; Zouboulis and Makrantonaki, 2011)

Conclusion

Different molecular mechanisms leading to direct and indirect increase in ROS are caused by intrinsic and extrinsic factors respectively and result in aging. Decreased level of dermal collagen and increased level of elastin in dermis result in the formation of wrinkles, disturbed skin texture and elastosis. The protective mechanism of shortening of telomeric length of chromosomes during each cell division results in cell senescence and serves as an indicator of aging. Various treatments and therapies from natural and synthetic sources are used to prevent skin aging.

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