Global Journals LaTeX JournalKaleidoscope™
Artificial Intelligence formulated this projection for compatibility purposes from the original article published at Global Journals. However, this technology is currently in beta. *Therefore, kindly ignore odd layouts, missed formulae, text, tables, or figures.*

Stop the Time for Your Skin: A Search for Aging Process

Harun Cerit[1], Engin Kozak[2] and Ipek Buyukipekci[3]

[1] Isstanbul University

Received: 8 December 2017 Accepted: 3 January 2018 Published: 15 January 2018

Abstract

One of the most common yet mis and poorly understood topic is ageing process and how it affects the body. Aging is a complex phenomenon that emerges in the coming years. Skin aging can be classified as intrinsic aging and extrinsic aging (photoaging). The skin changes over time due to decrease in hormone levels, chronic sun exposure, chronic inflammation and many other reasons. It occurs at microscopic level with physiological, histological and metabolic changes, at macroscopic level with wrinkles, dryness, loss of elasticity and stain formation. Delaying skin aging and alleviating the signs of aging with cosmetic products is one of the most important tasks of cosmetic science. The use of topically applied cosmeceuticals containing ingredients that affect deep biological functions has increased significantly in recent years. Antiaging cosmetic products used in facial care should be scientifically proven products whose efficacy and reliability are intended to show anti-aging effects using different biologically active ingredients. It is the intention of this article to review which biomolecules cause aging, why they cause it, and which crops can prevent unwanted problems caused by aging.

Index terms— aging, anti-aging, skin elasticity, herbal medicine, testosterone, estrogen, physical characteristic, hyaluronic acid, photo aging.

1 I.

What is Aging Process? ging is the continual processes of wear and tear in body which affect us both physically and mentally. Aging is an inevitable life fact and one of the most reputable problem of the current century. With its symptoms, almost all people have a fear of becoming old. Although symptoms of aging change person to person, loss of beauty in aesthetical features appears in general. While getting old, people face with growing white hair and hair loss, vision loss, hearing loss, skin deterioration, decay in posture, etc. In addition to these symptoms of physical appearance, the ones that cause health problems are far more important. While people get old, they become more susceptible to the age-related diseases like cancer, diabetes, cardiac dysfunctions, Alzheimer and many more. Those reasons can result in the decrease of self-confidence and life quality. Because of that, being young is the best way to live a healthy life with a sharp memory, strong muscles, good-looking physical appearance, good health, healthy brain and efficient immune system.

Even if people argue over what drives any or all of those processes, they all seem to agree on how they Author ?: e-mail: hcerit@istanbul.edu.tr affect us; they make us prone to falling apart. Not surprisingly, aging has a long history of humankind and their cultural traditions. [1] II.

2 Theories that Explains Aging Process

Even though there are a lot of theories for the explanation of the process of aging, none of them are fully convincing. Traditional ones support that aging is not an adaptation or genetically programmed. Modern biological theories of aging divided into two main categories which are programmed and damage or error. Programmed theory divided into three sub-categories but the main idea is aging is a continuation of growth and development which follows a biological timetable. In damage and error theories, aging is a result of an

environmental assault which induces cumulative damage on living organisms. [2] The free radical theory proposes that tissues and cells are damaged by the oxidative respiration as a result of aerobic metabolism. There are couple of evidence to support that: lifetime of the species depends on the metabolism rate and antioxidant activity which is protective to the body; increased production and expression of antioxidative enzymes can affect the lifetime of species; cellular level of free radical damage that is caused by some of the molecules, increases in time; additional or excessive calorie intake which causes extra free radicals also reduce the lifetime. [3] III.

3 Main Biochemical Processes in Antiaging

The biochemical processes that involved in aging are oxidation, glycation, and methylation. Other appropriate processes are chronic inflammation and hormonal deregulation.

4 a) Oxidation

Free radicals are produced by oxidation in oxygen metabolism within cells. They are a simple compound with an electron missing from their chemical structure which makes them unstable. Because of that, they seek out other chemical structures, so that they can acquire an electron and make the other structure unstable. The defense mechanism against free radicals is inactivating them after the production, removing them from antioxidants and increasing the elimination of material Which already damaged by free radicals. Free radicals damage the cell membrane which is composed of lipids and proteins. Their interaction with proteins and lipids causes the production of malondialdehyde which is very harmful, contributing to another aging process called glycation.

5 b) Glycation and Carnisone

Glycation is the attachment of glycose, fructose, and other sugar molecules to proteins. The binding between sugar and protein results in a cross-linking of proteins. Cross-linked proteins cause more damage by reacting with free radicals and other toxins. In addition to proteins, glycation reactions affect DNA too, resulted in cross linked DNA molecules which are no use at all. Dipeptide carnosine (b-alanyl-L-histidine), discovered a century earlier, is found in animal tissue, especially in muscle and brain, and sometimes in millimolar concentrations. There is increasing evidence that carnosine may be an effective anti-gelling agent, at least in model systems and cultured cells. Dipeptide can be used to inhibit the formation of protein carbonyls and to inhibit the formation of crosslinks induced by reducing sugars and other reactive aldehydes, malondialdehyde, and methylglyoxal. [4] Carnosine has some healing effects on aging, cellular and all animal levels. Carnosine suppresses aging in cultured human fibroblasts and even plays older cells. More recently, carnosine has been shown to protect the telomeres of cultured cells against oxidative damage. The beneficial effects of carnosine agingaccelerated mice on the survival, Drosophila and rodent fibroblasts was alsodescribed. [4]

6 c) Methylation

Methylation is the addition of methyl groups to proteins, DNA, and other molecules to keep them in good and active condition. Increased level of homocysteine reflects low methylation that is found indiabetes and heart disease. Increased intake of methylators reduces the risk of these diseases.

7 d) Chronic Inflammation

Chronic inflammation is the process of destruction of body tissues by toxic chemicals. Results in dementia, thickening of the arteries, diabetes, hormonal imbalance and others.

Recent data indicate that systemic aging can be affected by inflammation with neuroendocrine markers3. At a tissue level, inflammation may contribute to senescence 5,6,7 in progeria mouse models4 and DNA damage, indicating synergistic interactions between DNA damage responses (DDRs) and inflammatory signals.

Latest data show that systemic aging might be influenced by inflammation via neuro-endocrine signaling [5] . On a tissue level, inflammation might contribute to aging in mouse skin [6] and in DNA damage-driven progeria mouse models [7,8,9] , suggesting synergistic interactions between DNA damage responses (DDRs) and inflammatory signals.

8 e) Hormonal Deregulation

Hormonal deregulation is an important factor in aging since hormones are needed to be replaced and reactivated during aging to prevent the body from falling apart [10] .

9 f) Proteins

The most common symptom of aging at the molecular level is the accumulation of altered proteins both in and out of cells; The modifications may be in either the polypeptide chain length or the amino acid composition. Modified proteins are produced continuously, both biosynthetically and synthetically.

Altered proteins are also associated with many age-related pathologies such as Alzheimer's disease (AD), Parkinsons' disease (PD), cataractogenesis, atherosclerosis, diabetic secondary complications, etc. Consequently,

it is thought that these accumulations are possibly causative to much age-related pathology and interventions to either prevent the production of the altered protein forms or facilitate their removal could delay certain age-related diseases [4] .

10 g) Photoaging

Chronic exposure to the sun leads to the photoaging of human skin, a process characterized by clinical, histological, and biochemical changes that are chronologically elongated. In recent years significant progress has been made in resolving the underlying mechanisms of photography. Recently, the induction of matrix metalloproteinases as a consequence of activator protein (AP) -1 and nuclear factor (NF) -KB activation and mitochondrial DNA mutations has been described [11] .

11 IV.

What is Anti-Aging?

Anti-aging means prevention or limitation of the process of becoming old. Furthermore, the meaning of anti-aging changes in medical and scientific fields. In the scientific field, anti-aging refers to prevention, deceleration, or reversion of aging process. In the medical field, it refers to early detection, prevention, and treatment of age-related diseases. For instance, heart diseases are age related and a treatment method that do not effect on the aging process can help people to live longer and healthier lives. The treatment method is anti-aging according to medical fields. However, scientific fields do not approve [12] .

12 a) Applications of anti-aging

There are a lot of different types of applications of anti-aging like; ? Without addressing aging, treatment a specific disease.

? Slowing down aging process by preventing or delaying physiological decline and regaining lost functional abilities. ? Cosmetic treatments.

? Altering our bodies to improve the basic molecular and genetic processes of maintenance and repair to make them work more efficient, and longer. ? Use of the body's intrinsic capacity for selfmaintenance and repair **??**13] .

V.

What are the Key Molecules that used in Anti-Aging?

? Estrogen Sex hormones are involved in changes in skin texture, elasticity, and growth of hair. The effects of estrogen on human skin studied and results shows that it has a delaying or preventing effect on skin aging [14] .

In the skin, estrogens affect thickness, wrinkle formation and moisture. Estrogens may enhance glycosaminoglycan (GAG), such as Hyaluronic Acid, to maintain fluid balance and structural integrity. At the same time, they can increase the production of collagen, maintaining epidermal thickness and allowing the skin to remain fuller, hydrated and wrinkle-free. It is not the only external feature that utilizes skin from estrogens. In addition to revealing a fuller, healthy skin, estrogens can make your hair longer and healthier [15] .

13 a) Estrogens and the skin

Loss of estrogen in the menopause has a profound effect on the skin. Postmenopausal women have shown that estrogen treatment increases collagen content, skin thickness and elasticity, and the effect of estrogen on skin water content is also promising [16] .

14 ? Testosterone

Some of the effects of testosterone treatments are studied and by the results, it is clear that testosterone treatment to increase lean body mass, decrease visceral fat mass, increase bone mineral density, and decrease total cholesterol for aging hypogonadal men [17] . Rougher hair, thicker and oilier skins, and usually a sign of skin aging, is linked to testosterone. Female paternal alopecia or baldness is associated with increased androgen levels and is the most common cause of hair loss in women. With age, the ratio of estrogen-androgen 3 becomes unbalanced, and changes occur after menopause. Since androgens and especially testosterone are involved in skin sebum production, increased fatness or even adult acne may occur when hormones become unbalanced during menstruation or menopause in women. The effects of androgens on the skin are important in both male and female patients, both of which may be affected by varying levels of androgens [15] .

15 b) Testosterone delays vascular smooth muscle cell (VSMC) senescence and inhibits collagen synthesis

In this study, muscular mechanism of testosterone in protecting against VSMC senescence was found. Results showed that testosterone plays a fundamental role in cell senescence which could be a critical mechanism for delaying vascular aging [18] c) Testosterone increases renal anti-aging klotho gene expression via the androgen receptor-mediated pathway They found that renal klotho mRNA and protein expression were significantly reduced

in the aging kidneys of male mice that have a lower serum testosterone level and lower AR expression than young mice. Moreover, testosterone supplement up-regulated both klotho and AR expression in testosterone-deficient ORX mice and in NRK52E cells, suggesting that renal klotho mRNA expression may be regulated by testosterone in an AR-dependent mechanism [19] ? Phytochemicals Phytochemicals are secondary plant metabolites that present in food, fruits, vegetables, nuts, cocoa, beverages and many more. Abilities of many phytochemicals have been studied and they have been found that they have an effect on the prevention and treatment of diseases like cancer, cardiovascular disease, diabetes, obesity, Alzheimer and other neurological dysfunctions [20] Betanin is a sub group of one of the seven main categories of phytochemicals, betalains. It presents in beets and chard.

16 d) Effect of betanin on a rat paraquat-induced acute lung injury (ALI)

In this study, paraquat was injected intraperitoneally at a single dose and betanin was orally administered 3 days before and 2 days after paraquat administration. Rats were sacrificed 24 hours after the last betanin dosage, and lung tissue and bronchoalveolar lavage fluid (BALF) were collected. In rats treated only with paraquat, extensive lung injury characteristic of ALI was observed. In rats treated with betanin, paraquat-induced ALI was attenuated in a dose-dependent manner [21] e) Effect of betanin on reducing accumulation and crosslinking of collagen in high-fructose-fed rat heart Because of its antagonizing effect with insulin resistance, according to this study; betanin treatment reduces the cardiac collagen accumulating, crosslinking and inhibited profibrotic factor-TGF-B1 and CTGF protein expression in fructose-fed rat heart [22] f) Betanin attenuates carbon tetrachloride (CCl4)induced liver injury in common carp (Cyprinus carpio L.) This study, protective effect of betanin against liver injury induced by carbon tetrachloride (CCl4) in common carp was investigated. The fish were treated with betanin in fodder throughout the experiment. After 20 days of treatment, the fish were intraperitoneally injected with CCl4, and were killed three days after CCl4 intoxication, and then, histological and biochemical assays were performed. Results showed that CCl4induced liver CYP2E1 activity, oxidative stress, and injury, as indicated by the depleted glycogen storage, increased serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) activities and liver histological damage. Compared with the CCl4 control group, the betanin-treated groups exhibited, increased liver antioxidative capacity (increased glutathione level and superoxide dismutase and catalase activities), increased liver glycogen storage, reduced CYP2E1 activity, decreased malondialdehyde level, and reduced serum AST/ALT activities, with significant differences in the 2 and 4 groups (p\0.05). In conclusion, betanin attenuates CCl4-induced liver damage in common carp. Moreover, the inhibition CYP2E1 activity and oxidative stress may have significant roles in the protective effect of betanin [23] ? Hyaluronic acid Hyaluronic acid is a polysaccharide which is a part of the glycosaminoglycan family. It consists of a basic unit of two sugars, glucuronic acid, and N-acetylglucosamine. As a result of senescence, size of the HA polymers in the skin decreases over time [24] .Thus the epidermis loses the principle molecule responsible for binding and retaining water molecules, resulting in loss of skin moisture.

17 g) Hyaluronic acid and wound healing

In this study, an experiment model of ethanolinduced dermatotoxicity and hepatocytoxicity using normal human keratinocytes and normal human hepatocytes that preserve inducible cytochrome p450 activities was developed. Results showed that hyaluronic acid could be used safely for skin regeneration. Both alone and combination with herbals choices are viable [25,26] .

18 ? Melatonin

Melatonin has a favorable influence on the aging process because it has an inverse effect with regard to body weight; food restriction raises the levels of melatonin and decreases its age-related decrease. With increasing age comes a decrease of melatonin production, which may have a connection to sleep disorders suffered by elderly people. It also was shown that melatonin can prevent the tumor development and growth. Interestingly, a study showed that patients with the tumor has a low level of melatonin compared to healthy individuals [27,28] .

h) What are the herbs that can or might affect aging process Some of the herbs defining as anti-aging herbs. Especially in Asian countries, medical herbs have a long history of usage as medicine. Anti-aging herbs have different effects on the body; they can boost the level of vital energy, act as food to provide essential nutrients, can be used for therapeutic effects [29] . Aloe vera L. (Family: Liliaceae) Aloeverais known for its medicinal uses for a very longtime. The usefulness of the plant was proven for minor burns and sunburns. However, medical and cosmetic effectiveness is still studying among scientist.

It has been shown that Alloin (1) and B inhibit Clostridium histolyticum collagenase in a reversible and reciprocal manner. Both aloe gel and alloin are also effective inhibitors of stimulated granulocyte MMPs [30] . It has been reported to modulate melanogenesis through the competitive inhibition of aloesin [2-acetonyl-8-betaglucopyranosyl-7-hydroxy-5-methylchromone], tyrosinase, isolated from A. vera. Tyrosine hydroxylase and 3,4-dihydroxyphenylalanine oxidase activities of tyrosinase from normal human melanocyte cell lysates were inhibited by aloesin in a doza-dependent manner [31] . Camellia japonica L. (Family: Theaceae) The anti-aging properties of C. japonica oil have been reported in human dermal fibroblast cells due to concentration in the

analysis of the human COL1A2 promoter luciferase [32] . Human type I procollagen synthesis was found to be induced by C. japonica oil while MMP-1 activity was inhibited. C. japonica oil can also retain trans-epidermal water loss (TEWL) without any side effects. Camellia sinensis L. (Family: Theaceae) Originally cultivated in East Asia, this plant grows as large as a shrub. Sunscreen formulated with 2-5% green tea extract has been reported to protect UV irradiation induced photoaging, photoimmunosuppression, cutaneous erythema, thickening of the epidermis, over expression of CK5/6, CK16, MMP-2, MMP-9, etc . [33] . A double-blind, placebo-controlled trial has been executed with moderate photoaging treated with either a combination regimen of 10% green tea cream and 300 mg twice-daily green tea oral supplementation or a placebo regimen for eight weeks to monitor the clinical and histologic appearance of photoaging skin [34] . Patients treated with topical as well as oral combination regimens have shown histological improvement in tissue elasticity, but no clinically significant changes have been found and may require a longer reinforcement for clinically observable developments. Green tea polyphenols have been reported to be suitable sunscreen to protect the skin from adverse effects such as catechin, epigallocatechin, epiglutocatechin-3gallate, etc., caused by UV radiation, inflammation, oxidative stress and DNA damage. skin cancer risk [35] .

Curcuma longa L. (Family: Zingiberaceae) C. longa extract has been found to make potential changes in skin thickness, elasticity, pigmentation and wrinkles caused by long-term, low-dose UV-B irradiation in melanin-containing hairless mice [36] . It prevents wrinkle and melanin formation and increases in the diameter and length of the skin blood vessels and reduces matrix metalloproteinase-2 (MMP-2) expression. For this reason, skin rash can be reduced with curcumin. Glycine max L.Merr (Family: Fabaceae) Anthocyanin isolated from black soybean seed responsible for downregulation of in vitro and in vivo UVB induced reactive oxygen species levels and apoptotic cell death through the prevention of caspase-3 pathway activation and reduction of proapoptotic Bax protein levels [37] .Finding highlights that anthocyanin from the seed coat of black soybean is useful compounds to modulate UVBinduced photoaging.

dulcis Mill. (Family: Rosaceae) The role of almond oil in reducing the degradative changes induced in skin upon exposure to UV radiation has been proposed and illustrated that biochemical parameters, glutathione, and lipid peroxidation have been ameliorated by almond oil [38] . Vaccinium uliginosum L. (Family: Ericaceae) Fruits of bog blueberry (V. uliginosum) are rich in anthocyanins like cyanidin-3-glucoside, petunidin-3-glucoside, malvidin-3-glucoside, and delphinidin-3-glucoside which have been documented for pigmentation and attenuation of photoaging through removal of reactive oxygen species (ROS) production and the resultant DNA damage responsible for activation of p53 and Bad in UV-B-irradiated human dermal fibroblasts [39] . Zingiberofficinale L. (Family: Zingiberaceae) Topical application of Z. officinale extract to hairless mouse skin significantly inhibited the wrinkle formation induced by chronic UV-B irradiation at a suberythemal dose accompanied by significant prevention of the decrease in the skin elasticity [40] . [1]

[1]

[(2001)] , 10.1016/s0034-5687(01. Feb. 2001. p. .

[Wickens] 'Ageing and the Free Radical Theory'. Andrew P Wickens . *Respiration Physiology* 128 (3) p. 28.

[Rattan, S. I. S. ()] 'Anti-ageing strategies: prevention or therapy?'. *Fight Aging!* Rattan, S. I. S. (ed.) 2 Apr. 2016. 2005. 13 (6) p. . (EMBO Reports. Suppl 1)

[Ho (2009)] 'Anti-Aging Herbal Medicine-How and Why Can They Be Used in Aging-Associated Neurodegenerative Diseases?'. Yuen-Shan Ho . *Ageing Research Reviews* 13 Oct. 2009. Elsevier.

[Arora ()] 'Anti-aging medicine'. B P Arora . *Indian Journal of Plastic Surgery : Official Publication of the Association of Plastic Surgeons of India* 2008. 41 p. . (Suppl)

[Arora ()] 'Anti-aging medicine'. B P Arora . *Indian Journal of Plastic Surgery: Official Publication of the Association of Plastic Surgeons of India* 2008. 41 p. . (Suppl)

[Han et al. ()] *Betanin attenuates carbon tetrachloride (CCl4)-induced liver injury in common carp (Cyprinus carpio L.). Fish PsysiolBiochem*, J Han , C Gao , S Yang , Wang J Tan , D . 2014. p. .

[Han et al. ()] 'Betanin reduces the accumulation and cross-links of collagen in high-fructose-fed rat heart through inhibiting non-enzymatic glycation'. J Han , C Tan , Y Wang , Yang S Tan , D . *Chem Biol Interact* 2015. p. .

[Bae et al. ()] 'Bog blueberry anthocyanins alleviate photoaging in ultraviolet-B irradiation induced human dermalfibroblasts'. J Y Bae , S S Lim , S J Kim , J S Choi , J Park , S M Ju , S J Han , I J Kang , Y H Kang . *Mol. Nutr. FoodRes* 2009. 53 p. .

[Si and Liu ()] 'Dietary antiaging phytochemicals and mechanisms associated with prolonged survival'. H Si , D Liu . *The Journal of Nutritional Biochemistry* 2014. 25 (6) p. .

[Chiu et al. ()] 'Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin'. A E Chiu , J L Chan , D G Kern , S Kohler , W E Rehmus , A B Kimball . *Dermatol. Surg* 2005. 31 p. .

[Jung et al. ()] 'Effect of Camellia japonica oil on human type I procollagen production and skin barrier function'. E Jung , J Lee , J Baek , K Jung , J Lee , S Huh , S Kim , J Koh , D Park . *J. Ethnopharmacol* 2007. 112 p. .

[Sultana et al. ()] 'Effect of pre-treatment of almond oil on ultraviolet B-induced cutaneous photoaging in mice'. Y Sultana , K Kohli , M Athar , R K Khar , M Aqil . *J. Cosmet. Dermatol* 2007. 6 p. .

[Saerompark et al. ()] 'Effective Anti-aging Strategies in an Era of Super-aging'. Min-Ji Saerompark , So-Nyeong Yang , Jeong-Sang Ha , Lee . *J Menopausal Med* 2014. 20 p. .

[Sumiyoshi and Kimura ()] 'Effects of a turmeric extract (Curcuma longa) on chronic ultraviolet B irradiation induced skin damage in melanin-possessing hairless mice'. M Sumiyoshi , Y Kimura . *Phytomedicine* 2009. 16 p. .

[Thornton ()] 'Estrogens and aging skin'. M J Thornton . *Dermato-Endocrinology* 2013. 5 (2) p. .

[Brincat (2005)] 'Estrogens and the Skin'. M P Brincat . *Climacteric: The Journal of the International Menopause Society* June 2005. U.S. National Library of Medicine

[Hipkiss (2005)] 'Glycation, Ageing and Carnosine: Are Carnivorous Diets Beneficial'. Alan R Hipkiss . *Mechanisms of Ageing and Development* June 2005. Elsevier. p. 13.

[Aguirre ()] *Hormones and Your Skin. The International Dermal Institute*, Claudia Aguirre . 2015.

[Neuman et al. ()] 'Hyaluronic Acid and Wound Healing'. Manuela G Neuman , Radu M Nanau , Loida Oruña-Sanchez , Gabriel Coto . *J Pharm Pharm Sci* 2015. 18 p. .

[Papakonstantinou and Roth (2012)] 'Hyaluronic Acid: A Key Molecule in Skin Aging'. Eleni Papakonstantinou , Michael Roth . *Dermato Endocrinology* 1 July 2012. Taylor & Francis.

[Zhang ()] 'Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH'. G Zhang . *Nature* 2013. 497 p. .

[Barrantes and Guinea ()] 'Inhibition of collagenase and metalloproteinases by aloins and aloe gel'. E Barrantes , M Guinea . *Life Sci* 2003. 72 p. .

[Tsukahara et al. ()] 'Inhibition of ultraviolet-B-induced wrinkle formation by an elastase-inhibiting herbal extract: implication for the mechanism underlying elastase-associated wrinkles'. K Tsukahara , H Nakagawa , S Moriwaki , Y Takema , T Fujimura , G Imokawa . *Int. J. Dermatol* 2006. 45 p. .

[Jones et al. ()] 'Modulation of melanogenesis by aloesin: a competitive inhibitor of tyrosinase'. K Jones , J Hughes , M Hong , Q Jia , S Orndorff . *Pigment Cell Res* 2002. 15 p. .

[Adler ()] 'Motif module map reveals enforcement of aging by continual NF-kB activity'. A S Adler . *Genes Dev* 2007. 21 p. .

[Han et al. ()] *Natural Antioxidant Betanin Protects Rats from Paraquat-Induced Acute Lung Injury Interstitial Pneumonia*, Junyan Han , Deshun Ma , Miao Zhang , Xuelian Yang , Dehong Tan . ID 608174. 2015. 2015.

[Tilstra ()] 'NF-?B inhibition delays DNA damage-induced senescence and aging in mice'. J S Tilstra . *Clin. Invest* 2012. 122 p. .

[Wetterberg et al. ()] 'Normative melatonin excretion: a multinational study'. L Wetterberg , J D Bergiannaki , T Paparrigopoulos , L Von Knorring , Eberhard G Bratlid , T . 10.1016/S0306-4530(98)00076-6. *Psychoneuroendocrinology* 1999. 24 p. .

[Osorio ()] 'Nuclear lamina defects cause ATM-dependent NF-?B activation and link accelerated aging to a systemic inflammatory response'. F G Osorio . *Genes Dev* 2012. 26 p. .

[Berneburg (Dec)] 'Photoaging of Human Skin'. M Berneburg . *Photodermatology, Photoimmunology & Photomedicine* Dec. U.S. National Library of Medicine

[Tsoyi et al. ()] 'Protective effect of anthocyanins from black soybean seed coats on UVB-induced apoptotic cell death in vitro and in vivo'. K Tsoyi , B P Hyung , M K Young , I L C Jong , C S Sung , J S Hae , S L Won , G S Han , H L Jae , C C Ki , J K Hye . *J. Agric. Food Chem* 2008. 56 p. .

[Li et al. ()] 'Protective effects of green tea extracts on photoaging and photommuno suppression'. Y H Li , Y Wu , H C Wei , Y Y Xu , L L Jia , J Chen , X S Yang , G H Dong , X H Gao , H D Chen . *Skin Res. Technol* 2009. 15 p. .

[Blask et al. ()] 'Putting cancer to sleep at night: the neuroendocrine/circadian melatonin signal'. D E Blask , R T Dauchy , L A Sauer . 10.1385/ENDO:27:2:179. *Endocrine* 2005. 27 p. .

[Kawahara ()] 'SIRT6 links histone H3 lysine 9 deacetylation to NF-?B-dependent gene expression and organismal life span'. T L A Kawahara . *Cell* 2009. 136 p. .

[Nichols and Katiyar ()] 'Skin photo protection by natural polyphenols: Antiinflammatory, antioxidant and DNA repair mechanisms'. J A Nichols , S K Katiyar . *Arch. Dermatol. Res* 2010. 302 p. .

[Chen et al. ()] 'Testosterone delays vascular smooth muscle cell senescence and inhibits collagen synthesis via the Gas6/Axl signaling pathway'. Y Chen , J Zhao , C Jin , Y Li , M Tang , Z Wang , M Zhong . *Age* 2016. 38 (3) p. 60.

[Stanworth and Jones ()] 'Testosterone for the aging male; current evidence and recommended practice'. R D Stanworth , T H Jones . *Clinical Interventions in Aging* 2008. 3 (1) p. .

[Hsu et al. ()] 'Testosterone increases renal anti-aging klotho gene expression via the androgen receptormediated pathway'. Shih-Che Hsu , Shih-Ming Huang , Shih-Hua Lin , Shuk-Man Ka , Ann Chen , Meng-Fu Shih , Yu-Juei Hsu . *Biochemical Journal* 2012.

[Stefánsson (2005)] 'The Science of Ageing and Anti-Ageing'. H Stefánsson . PMC1369276. *EMBO Reports* 6 July 2005.