Review Article

Anti-Aging - An Overview

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ABSTRACT

Skin aging is a biological complex process influenced by a combination of intrinsic and extrinsic factors. The fact is that the skin health and beauty is considered as major principal factor representing "Health" and "Well-being" in humans. Several skin aging treatments have been developed in recent years. The main objective of this article is to review about the most important anti-aging strategies that a dermatologists have in their hands now-a-days, such as preventive measures, cosmetological strategies, topical and systemic therapeutic agents and invasive procedures. Still research needed in this area to fully elucidate the molecular basis of the deteriorative changes during skin aging.

Keywords: Anti-aging, Antioxidants, Laser, Peeling, Fillers, Hormone replacement therapy, Cell regulators, Prevention.

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INTRODUCTION

Skin or is a part of natural human "aging mosaic" which becomes evident and follows different trajectories in different organs, tissues and cells with time. While the aging signs of internal organs are masked from the ambient "eyes", the skin provides first obvious marks of the passing time.[1] The intrinsic and extrinsic factors lead together to cumulative structural and physiological alterations and progressive changes in each skin layer as well as changes in skin appearance, especially on the sun exposed skin areas.[2] Gradual loss of skin elasticity leads to the sagging phenomenon.[3] Slowing of the epidermal turnover rate and cell cycle lengthening coincides with a slower wound healing and reduced effective desquamation in older adults.[4] On the other hand, many of these characteristic features are targets to product application or procedures to accelerate the cell cycle, in the belief that a faster turnover rate will yield improvement in skin appearance and will speed wound healing.[5] The sparse distribution and decrease in collagen content in photoaged skin can be due to increases collagen degradation by various matrix metalloproteinases, serine, and other proteases irrespective of the same collagen production.[6] The overall collagen content per unit area of the skin surface is known to decline approximately 1% by year.[7] Three primary structural components of the dermis, collagen, elastic, and Glycosaminoglycan (GAGs) have been the subjects of the majority of anti-aging research and efforts for aesthetic-anti-aging strategies pertaining to the skin, from "anti-wrinkle creams" to various filling agents.[8] Regardless of the fact that skin aging is a biological process and but not a pathological condition, including degenerative disorders, benign and malignant neoplasms.[9] The mainspring of any skin anti-aging therapy is to achieve a healthy, smooth, blemish-free, translucent and resilient skin.[10] In the clinical practice it is very important to understand the patient's wishes and to gives the satisfying results after the treatment.[11] The age, previous surgery, general health status, type of the skin, style of life and other factors also should be considered before giving the skin ageing treatment. This review will emphasize the most important topical and systemic therapeutic agents and trends in the use of invasive procedures.

Skin Aging Prevention and Therapy

The skin anti-aging strategies and treatments is done to reverse the dermal and epidermal signs of photo and chronological aging can be grouped by the following (table 1).

Skin anti-aging approaches:

Table 1: changes in intrinsic aging and extrinsic aging factors

Cosmetological care	Daily skin care, Correct sun protection, aesthetic non-invasive procedures, Chemical peelings, Visible light devices, Intense pulsed light (IPL), Ablative and non-ablative laser photo-rejuvenation, Radiofrequency (RF)
Topical medical agents or topical agents	Antioxidants, Cell regulators.

Invasive procedures	Injectable skin bio-stimulation and rejuvenation, prevention of dynamic wrinkles, correction of static, anatomical wrinkles, restoration of fat and volume loss, skin augmentation and contouring.
Systemic agents	Hormone replacement therapy
Avoiding of exogenous factors of aging, correction of life style and habits	Smoking, pollution, solar UV irradiation. Stress, nutrition, diet restriction and alimentary supplementation, physical activity, control of general health.

Table 2: Intrinsic and Extrinsic factors

Intrinsic Factors	Extrinsic Factors
Increased catabolism states (burns and wounds)	Photoaging (sunlight or UV exposure)
Insufficient intrinsic antioxidant protection.	Environmental intoxication (Smoking, industrial pollution, heavy metals, detergents)
Insufficient melanin production = increased susceptibility to UV aging.	Prolonged inflammation (chronic infection, auto-immune disorders)
Insufficient detoxification function = higher vulnerability to toxic substances.	Poor diet (saturated fats, food additives, alcohol, insufficient water intake)
Sexual hormone deficiency.	Lack of sleep or poor sleep hygiene.
Impaired energy metabolism	Stress (physical, emotional: exams)

Photoprotection and Systemic Antioxidant

Chronic photodamage of skin manifests itself as extrinsic skin aging. DNA photodamage & UV-generated reactive oxygen species are initial molecular events that cause most of the typical histological & clinical manifestations of chronic photodamage of the skin. Wrinkling pigmentary changes are directly associated with premature photoaging and are considered its most important cutaneous manifestations. The strategies aimed to prevent p h01 otoaging are sun avoidance, sun protection using sunscreens to block or to reduce skin exposure.

UV radiation and retinoids in order to inhibit collagenase synthesis and to promote collagen production and anti-oxidants mainly in combination to reduce & neutralize the free radicals.[12] Interventional studies prove that it was in fact possible to delay skin aging

& to improve skin condition through the administration of specific nutritional supplements. Nutritional anti-oxidants acts through different compartments and by different mechanisms, but are mainly free radical (FR) scavengers:

1. They directly neutralize FR.
2. They reduce the peroxide concentration and repairs oxidized membranes.
3. They quench iron to reduce ROS production.

Via lipid metabolism, short chain free fatty acids and cholesteryl esters neutralize ROS.[13] Most of the anti-oxidants are categorized under vitamin C, vitamin E, carotenoids & trace elements of copper and selenium[14]. There are some studies which concluded that the combination of vitamin C and E on reacting with ferulic acid produces both sunscreen and anti-oxidant effect.[15]

Molecular mechanisms in skin aging

There are various models which are proposed to explain the molecular basis for skin aging, including the theory of cellular senescence, decrease in cellular DNA repair capacity and loss of telomeres, oxidative stress, single gene mutation, reduced sugar, caused by extrinsic factors and only 3% of aging factors intrinsic background.[16] Here important models and development in molecular mechanism research are highlighted on skin aging.

Oxidative stress

The reactive oxygen species (ROS) play a vital role in cutaneous extracellular matrix changes in both photoaging and intrinsic aging. ROS can be produced from different sources such as the mitochondrial electron transport chain, peroxisomal and endoplasmic reticulum localized proteins and such enzymes as cyclooxygenases, lipoxygenases, xanthine oxidases, and NADPH.[17] Activated NF-kB and AP-1 repress collagen production and increase MMP gene transcription, which results in the decrease of collagen content in photoaged skin.[18]

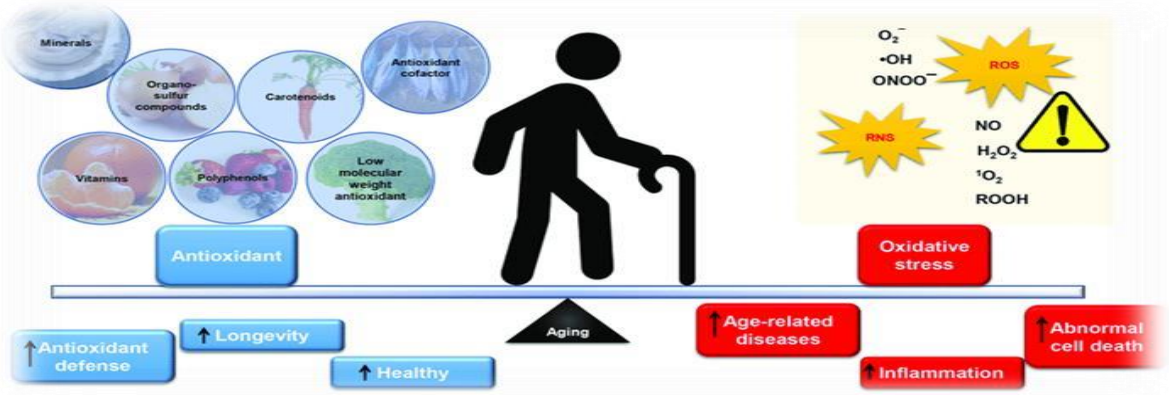

Figure 1: Molecular mechanism in skin aging.

DNA Damage

When dermis is exposed to UV radiation increases DNA damage, mutations and leads to carcinogenesis.[19] When DNA absorbs photons from UV-B resulting in defects of DNA strands.[20] DNA damage can be repaired by removing the lesion by photolyase enzyme, but human cells lack this enzyme.[21] Various studies proved with evidence that the use of sunscreen prevents DNA damage and protects the skin from carcinoma and melanoma.[22]

Telomere shortening

Telomeres are repetitive nucleotide sequences that cap and save the ends of chromosomes from degradation and abnormal recombination. When the cell division takes places then it becomes shorter by each division and results in limited number of cell division.[23] Telomerase is an enzyme that promotes telomere repetitions to the end to prevent telomeres from getting shorter. Moreover, proliferation capacity of epidermal stem cells with short telomeres was decreased, whereas telomerase reintroduction in mice with critically short telomeres is sufficient to correct epidermal stem cell defects.[24] UV radiation leads to excessive ROS production, which results in telomere mutations and leads to further cell death.[25]

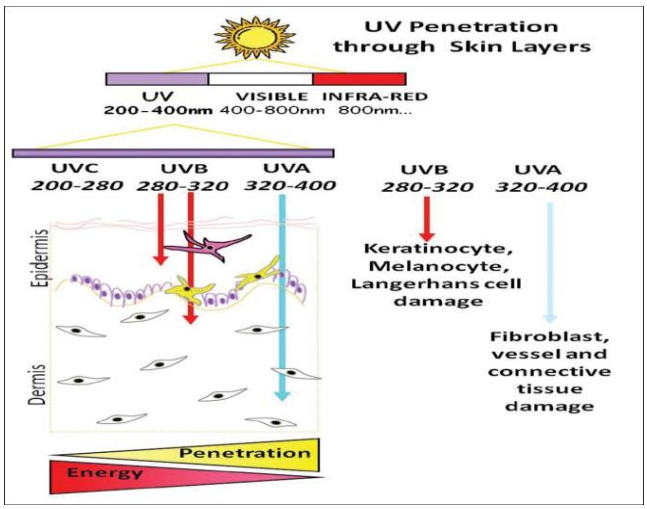

Figure 2: UV penetration through skin layers

Inflammaging

Chronic, low-grade inflammation is also estimated as a main characteristic of the aging process.[26] This phenomenon is called as "Inflammaging". Inflammaging plays a role in the progression of age-related diseases such as type II diabetes, Alzheimer's diseases, cardiovascular diseases osteoporosis, and skin aging.[27] UV radiation promotes oxidative stress in epidermal cells, leads to damaged cells with oxidized lipids. Activated macrophages release MMP's to reduce extracellular matrix. Repeated exposure to UV radiation results in activation of complement system, causing damage to the dermisepidermis junction, on which they deposit, and macrophages are overburdened with oxidised lipids. Proinflammatory cytokines and ROS[28] are released from overburdened macrophages, when the chronic inflammation is caused then it leads to the long-term damage to the skin, while the latter triggers the oxidative stress-induced damage to the cutaneous extracellular matrix.

Topical pharmacological agents with anti-aging properties

There are two major groups of agents which can be used as anti-aging cream components, antioxidants and cell regulators. The antioxidants such as vitamins, polyphenols and flavonoids, reduces collagen degradation by decreasing concentration of Free Radicles in the tissues. The cell regulators for example, retinols, peptides and growth factor (GF), have direct effects on collagen production and collagen metabolism.

Vitamins C, B3 and E are the most predominant antioxidants because of their ability to enter or penetrate into the skin because it has small molecular weight.[29] Clinical studies have proven that the antioxidative protection is more with the combination of vitamins C and E than with the vitamin C and E alone.[30] Niacinamide regulates cell metabolism and regeneration, and it is used in 5% concentration as an anti-aging agent.[31] Vit E used as a component of skin products having anti-proliferative and anti-inflammatory effects in concentrations between 2% and 20%. These effects are not as strong as with vitamins C and B3.[32]

An in vivo study has proven that the topical application of green tea polyphenols before the exposure of UV leads to an increase of the minimal number of Langerhans cells and reduces DNA damage in the skin.[33] Other botanicals that act as antioxidants are the isoflavones from soya.[34]

Vitamin A or retinol and its derivates are a group of agents having antioxidant effects. Retinol is the substance that is most often used as an anti-aging compound and causes less skin irritation.[35] It shows that retinol has positive effect on collagen metabolism.[36] Tretinoin, a nonaromatic retinoid of the first generation, is approved for application for treatment of anti-ageing in a concentration of 0.05% in the United States. Through topical application, polypeptides have the ability to activate dermal metabolism and stimulate collagen synthesis.[37]

Invasive Procedures

There are various no of procedures, most of that which are intended to 'resurface' the epidermis: to remove the damaged epidermis and to replace that damaged epidermis with remodeled skin layers and sometimes spur the formation of new collagen.[38] It is possible that the potential of GF, cytokines and telomerase will be harnessed through technological advancement and innovation in the burgeoning fields of tissue engineering and gene therapy in the nearest future.[39]

Chemical Peels

These Chemical peels are the methods used to cause a chemical ablation of defined skin layers to induce an even and tight skin as a result of the repair mechanism and regeneration after the inflammation of the epidermis and

dermis. The Chemical peels are classified into three categories[40]

1.Superficial peels

2.Medium-depth peels

3.Deep peels

The depth of peeling does not depend on the substance used only pH of the solution and time of application.[41]

1. If superficial peelings target the corneosomes, cause desquamation, lead to epidermolysis and exfoliation, increases the epidermal activity of enzymes.[42]
2. Medium-depth peels cause coagulation of membrane proteins, destroys or degrades living cells of the epidermis and dermis.
3. Deep peels coagulate proteins and produces complete epidermolysis, restructure of the basal layer and restoration of the dermal architecture.[43,44]

Figure 3: Chemical peels.

Visible Light Devices: IPL, Laser, RF for Skin Rejuvenation, Resurfacing and Tightening

Nonablative skin rejuvenation comes as a low risk and short disruption of cutaneous integrity.[45] Nonablative skin rejuvenation is not an accurate term since rejuvenation is a controlled form the skin wounding aimed for achieving a more youthful appearance after the healing of wound.[46] Treatment of prolonged skin has been divided into treatment of ectatic vessels and erythema, irregular pigmentation, pilosebaceous changes and into the improvement of the dermal and subcutaneous senescence.[47] The epidermis and superficial dermis can be selectively damaged by two basic mechanisms:

1. By targeting discrete chromophores in the dermis or at the dermal-epidermis junction.

2. By utilizing mid infrared lasers.[48]

The devices for treatment of vascular or pigment irregularities include lasers emitting light at 532, 585, 595, 755, 800, 1064nm wavelengths as well as filtered light generated by IPL systems equipped with different cut-off filters.[49] The clinical efficacy of these nonablative modalities are of weaker than that of the ablative methods new collagen formation and clinically observable improvement in wrinkles can be observed.[50] Reduction of facial wrinkles by using IPL devices has shown less effect comparing to the laser technology,[51] but for type I photo rejuvenation, IPL systems have in general shown considerably better results compared to laser systems operating at sub purpuric energy levels.[52] An increase in grenz zone thickness,[53] monoclonal chondroitin sulphate and III procollagen staining as well as quantification of col-1[54] was measured after couple of treatments with PDL. The increase in skin collagen has also been confirmed by non-invasive ultrasonographic analysis[55] and radioimmunoassay.[56] Nonablative skin rejuvenation should not yet be considered an alternative for laser resurfacing.[57] However there are interesting data showing comparative histological changes between the ablative and nonablative modalities.[58]

Histological sections of skin before and after the treatment by using different IPL devices have shown the formation of new collagen in the papillary and reticular dermis, as well as an increase in the number of fibroblasts and proportional decrease in the amount of solar elastosis is also usually found.[59] Laser resurfacing has been shown to be effective in counteracting photoaging through entire epidermal ablation, collagen shrinkage, extensive dermal remodelling, regeneration of cellular organelles, stimulation of neocollagenesis, and intercellular attachments[60] but results in long recover time are associate with risks of severe long lasting side effects, such as persistent erythema, hypo or hyper pigmentation, infection.[61] These devices emit light in a pixilated fashion onto the skin, producing an array of microthermal zones in the dermis.[62] The controlled thermal stress to the epidermis and the dermal compartments is followed by a wound healing response ultimately leading to re-epithelization and dermal remodelling.[63] Type I and type III procollagen mRNA was also elevated for atleast 6 mo.[64]

Monopolar RF is a non-invasive way to obtain skin tightening[65] and immediate collagen contraction with a single treatment. The RF technology produces electric current, which generates heat through resistance in the dermis and as deep as the subcutaneous fat.[66] There is a lack of long-term studies of efficacy and analysis of side effects for the skin using this method of skin rejuvenation. It is obvious that various treatment modalities using visible light devices have resulted in varying clinical effects and allow to select individual treatment parameters for different indications.[67] Careful simultaneous evaluation of any cutaneous sagging pigment disturbances, wrinkles, vascular abnormalities, and pigment disturbances as dermal layers are all linked is highly recommended.

Injectable Skin Rejuvenation and Dermal Fillers

The main aim of skin or cutaneous bio rejuvenation is to increase or enhance the biosynthetic capacity of fibroblasts, inducing the reconstruction of an optimal physiologic environment, the enhancement of cell activity, hydration and the synthesis of collagen, elastin and hyaluronic acid. The desired effect could be achieved by the microinjection in the superficial dermis of products containing only one active ingredient and totally absorbable: HA, vitamins, minerals, nutrients, hormones, GF, amino acids etc.[68] The

distinct formulations can induce strikingly divergent molecular and cellular processes in fibroblasts in vitro.[69] Products injected under the skin to improve the physical features by soft tissue augmentation and are called as fillers.[70] There are autologous, collagen, HA, synthetic implants. These may be grouped into temporary, semipermanent or permanent materials. GAG and HA are the major important components of the skin extracellular matrix involved in repairing the tissues of all animal tissues.[71] HA exhibits no species specificity. As a physical background material, lubrication, shock absorption, protein exclusion. HA has been implicated as a regulator of cell proliferation (regeneration) and locomotion.[72]

Figure 4: Injectable skin rejuvenation and dermal fillers.

Natural HA has a half-life of only 1 or 2 days before undergoing aqueous dilution and enzyme degradation in the liver to CO_2 and water in the tissues.[73] Produced from bacterial fermentation and modified by chemical cross-linking to improve their resistance to enzymatic degradation and prolong their effect, non-animal reticulated HA fillers are more pure, more viscous, generally well tolerated and rarely elicit adverse and immunological reactions.[74] The duration of effect for HA fillers ranges from 3 to 12 mo. Modern HA fillers varies in particulate size, cross-linking and the type of crosslinking agent used in the HA.[75] One of long-lasting synthetic semi-permanent dermal fillers is calcium hydroxyl apatite based filler kept in an aqueous carboxymethylcellulose gel carrier.[76] The CaHA particles act as a scaffold for new tissue formation and stimulate collagen formation around the microspheres leading to a thickening of the dermis over time.[77] The spherical CaHA particles are generally phagocytosed, degraded as calcium and phosphate and eliminated through the renal system. The application of polylactic acid in soft tissue augmentation exploits a mechanism of action not seen in any other soft tissue filler like a treatment plan, preparation of injection material, injection technique is distinct as well.[78] After the first response lasting one week or less a delayed but progressive volumizing effect begins.[79] This inflammatory reaction causes dermal fibroplasia that leads to the desired cosmetic effect.[80]

Autologous platelet-rich plasma

Autologous platelet-rich plasma has attracted attention for skin rejuvenation. PRP is derived from fresh whole blood, which contains a high concentration of platelets.[81] Various GF, including platelet-derived GF, transforming GF, vascular endothelial GF and insulin like GF, are secreted from the alpha-granules of concentrated platelets activated by aggregation inducers.[82] These factors are known to regulate the processes including the cell migration, attachment, proliferation, and differentiation, and promote extracellular matrix accumulation by binding to specific cell surface receptors.[83] It has been shown that PRP may induce the synthesis of collagen and other matrix components by stimulating the activation of fibroblasts rejuvenating the skin.[84] The molecular mechanisms underlying PRP-inducing wound healing processes are still largely unknown and experimental studies confirming the effects of PRP on aged fibroblasts are very limited.

Treatments for Skin Aging

1. Antioxidants

Antioxidants as reducing agents can relieve skin aging by neutralizing ROS that have already formed. ROS activates MAPK pathway and subsequently increase MMP production that degrades collagen. This can be prevented by antioxidants, such as vitamin C and vitamin E, or antioxidative enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, and coenzymes Q10.[85] Some plants may also be used as the natural source of antioxidants, such as green tea and aloe vera.[86] A recent example is that epigallocatechin gallate (EGCG), a kind of catechin in green tea, prevents skin aging via the epidermal growth factor receptor (EGFR) pathway in an aging mouse model, resulting in better skin structure than the control.[87] Moreover N-acetylcysteine, the precursor to the antioxidant glutathione, seems to be successful in the treatment of vascular and nonvascular neurological disorders as well as against age-related decline in tissue regeneration.[88] indicating its prospective antiaging applications in skin.

2. Stem cell therapy

Stem cell transplantation is a promising therapy for the treatment of skin ageing. Adipose tissue transplantation could improve skin quality at the recipient site in addition to increasing skin volume.[89] Further experiments demonstrate that adipose derived stem cells contribute to the regeneration of skin during aging.[90] In recent clinical tests, autologous fat grafting rejuvenates aging skin and enhances the volume of periocular and perioral skin in recipients with an average age of 50 years.[91] Data show that ADSCs produce a series of growth factors, such as vascular endothelial growth factor, basic fibroblast growth factor, transforming growth factor TGF-β1, TGF-β2, hepatocyte growth factor, keratinocyte growth factor, platelet-derived growth factor AA and placental growth factor,[92] reminding us that ADSCs may influence surroundings cutaneous cells through these secretions. It seemed that ADSC may also transdifferentiate into epithelial stem cells that epithelial stem cell marker p63 after fat grafting.[93] This work provides clues into the understanding of how fat grafts may rejuvenate overlying skin.

3. Hormone replacement therapy

In addition to being used in the treatment of symptoms caused by menopause, hormone replacement therapy is used to slow the skin aging process. HRT improve skin thickness, collagen content, and elasticity and it enhances hydration. However, there are studies suggesting that HRT increases the risk of developing breast cancer.[94]

CONCLUSION

There is a contradiction between the irreversibility of skin aging and people's thirst for eternal young appearance. From ancient to modern times, many efforts were made trying to understand the truth of cutaneous aging and to prevent or even reverse the aging process. This review summarizes the structural changes in both intrinsically and extrinsically aged skin, main molecular mechanisms proposed to explain these phenotypes, and advances in treatment research. It seems that skin aging is brought about by the comprehensive effect of different mechanisms, and its difficult to develop an integrated theory to string different models together. Ambiguity in the molecular mechanism of skin aging, as well as controversy in viewpoints, retarded the progress of targeted therapy, although some therapeutic attempts have proven to be effective. As people's cosmetic requirements increase, more research efforts should persist to fully elucidate the molecular basis of the deteriorative changes during skin aging.

REFERENCES

1. Cevenini E, Invidia L, Lescai F, Salvioli S, Tieri P, Castellani G, et al. Human models of aging and longevity. Expert Opin Biol Ther. 2008 Sep;8(9):1393-405. DOI: 10.1517/14712598.8.9.1393; PMID: 18694357.
2. Uitto J. Understanding premature skin aging. N Engl J Med. 1997 Nov 13;337(20):1463-5. DOI: 10.1056/NEJM199711133372011; PMID: 9358147.
3. Escoffier C, de Rigal J, Rochefort A, Vasselet R, Lévêque JL, Agache PG. Age-related mechanical properties of human skin: an in vivo study. J Invest Dermatol. 1989 Sep;93(3):353-7. DOI:10.1111/1523-1747.ep12280259; PMID: 2768836.
4. Yaar M, Gilchrest BA. Aging of skin. In Fitzpatrick's Dermatology in General Medicine Vol 2, 5th edn. McGraw-hill:New York, 1999;1697-1706.
5. Baumann L. Skin ageing and its treatment. J Pathol. 2007 Jan;211(2):241-51. DOI; 10.1002/path.2098 ;PMID: 17200942.
6. Varani J, Spearman D, Perone P, Fligiel SE, Datta SC, Wang ZQ, et al. Inhibition of type I procollagen synthesis by damaged collagen in photoaged skin and by collagenase-degraded collagen in vitro. Am J Pathol. 2001 Mar;158(3):931-42. DOI:10.1016/S0002-9440(10)64040-0; PMID: 11238041.
7. Shuster S, Black MM, McVitie E. The influence of age and sex on skin thickness, skin collagen and density. Br J Dermatol. 1975 Dec;93(6):639-43. PMID: 1220811; DOI: 10.1111/j.13652133.1975.tb05113.x.
8. Baumann L. Skin ageing and its treatment. J Pathol. 2007 Jan;211(2):241-51.DOI: 10.1002/path.2098; PMID: 17200942.
9. Calasanti TM, Slevin KF, King N. Ageism and feminism: from 'et cetera' to center. NWSA J. 2006;18:13-30. DOI:10.2979/NWS.2006.18.1.13.
10. Vedamurthy M. Antiaging therapies. Indian J Dermatol Venereol Leprol. 2006 May-Jun;72(3):183-6.DOI: 10.4103/0378-6323.257 ;PMID: 16766830 76.
11. Dierickx CC, Anderson RR. Visible light treatment of photoaging. Dermatol Ther. 2005 May-Jun;18(3):191-208. DOI:10.1111/j.1529-8019.2005.05019.x ;PMID: 16229721.
12. Trautinger F. Mechanisms of photodamage of the skin and its functional consequences for skin ageing. Clin Exp Dermatol. 2001 Oct;26(7):573-7. DOI: 10.1046/j.1365-2230.2001.00893.x; PMID: 11696060.
13. Berger MM. Can oxidative damage be treated nutritionally. Clin Nutr. 2005 Apr;24(2):172-83. DOI: 10.1016/j.clnu.2004.10.003; PMID: 15784476.
14. Marini A. [Beauty from the inside. Does it really work?] *Hautarzt.* 2011;62:614–7. DOI: 10.1007/s00105-011-2138-5.
15. Lin FH, Lin JY, Gupta RD, Tournas JA, Burch JA, Selim MA, et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. J Invest Dermatol. 2005 Oct;125(4):826-32. DOI: 10.1111/j.0022-202X.2005.23768.x ; PMID: 16185284.
16. Poljšak B, Dahmane RG, Godić A. Intrinsic skin aging: the role of oxidative stress. Acta Dermatovenerol Alp Pannonica Adriat. 2012;21(2):33-6. PMID: 23000938.
17. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. Biomolecules. 2015 Apr 21;5(2):545-89. DOI: 10.3390/biom5020545; PMID: 25906193.
18. Kammeyer A, Luiten RM. Oxidation events and skin aging. Ageing Res Rev. 2015 May;21:16-29. DOI: 10.1016/j.arr.2015.01.001; PMID: 25653189.
19. Tsatsou F, Trakatelli M, Patsatsi A, Kalokasidis K, Sotiriadis D. Extrinsic aging: UV-mediated skin carcinogenesis. Dermatoendocrinol. 2012 Jul 1;4(3):285-97. DOI: 10.4161/derm.22519;PMID: 23467430.
20. Ravanat JL, Douki T, Cadet J. Direct and indirect effects of UV radiation on DNA and its components. J Photochem Photobiol B. 2001 Oct;63(1-3):88-102. DOI: 10.1016/s1011-1344(01)00206-8; PMID: 11684456.
21. Panich U, Sittithumcharee G, Rathviboon N, Jirawatnotai S. Ultraviolet Radiation-Induced Skin Aging: The Role of DNA Damage and Oxidative Stress in Epidermal Stem Cell Damage Mediated Skin Aging. Stem Cells Int. 2016;2016:7370642. DOI: 10.1155/2016/7370642; PMID: 27148370.
22. Olsen CM, Wilson LF, Green AC, Biswas N, Loyalka J, Whiteman DC. Prevention of DNA damage in human skin by topical sunscreens. Photodermatol Photoimmunol Photomed. 2017 May;33(3):135-42. DOI: 10.1111/phpp.12298; PMID: 28165636.
23. Panich U, Sittithumcharee G, Rathviboon N, Jirawatnotai S. Ultraviolet Radiation-Induced Skin Aging: The Role of DNA Damage and Oxidative Stress in Epidermal Stem Cell Damage Mediated Skin Aging. Stem Cells Int. 2016;2016:7370642. DOI: 10.1155/2016/7370642;PMID: 27148370.
24. Siegl-Cachedenier I, Flores I, Klatt P, Blasco MA. Telomerase reverses epidermal hair follicle stem cell defects and loss of long-term survival associated with critically short telomeres. J Cell Biol. 2007 Oct 22;179(2):277-90. DOI: 10.1083/jcb.200704141; PMID: 17954610
25. Buckingham EM, Klingelhutz AJ. The role of telomeres in the ageing of human skin. Exp Dermatol.2011Apr;20(4):297-302.DOI: 10.1111/j.1600-0625.2010.01242.x, PMID: 21371125.
26. Sinclair J, Sarai A, Garland S. A backflow of electrons around photosystem II in Chlorella cells. Biochim Biophys Acta. 1979 May 9;546(2):256-69. DOI: 10.1016/0005-2728(79)90044-6; PMID: 10911963.
27. Fougère B, Boulanger E, Nourhashémi F, Guyonnet S, Cesari M. Chronic Inflammation: Accelerator of Biological Aging. J Gerontol A Biol Sci Med Sci. 2017 Sep 1;72(9):1218-25. DOI: 10.1093/gerona/glw240; PMID: 28003373.
28. Takahara M, Kang K, Liu L, Yoshida Y, McCormick TS, Cooper KD. iC3b arrests monocytic cell differentiation into CD1c-expressing dendritic cell precursors: a mechanism for transiently decreased dendritic cells in vivo after human skin injury by ultraviolet B. J Invest Dermatol. 2003 May;120(5):802-9. DOI: 10.1046/j.1523-1747.2003.12136.x; PMID: 12713585.
29. Bissett DL, Miyamoto K, Sun P, Li J, Berge CA. Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented

spots in aging facial skin. Int J Cosmet Sci. 2004 Oct;26(5):231-8. DOI: 10.1111/j.1749-6632.2000.tb06651.x;PMID: 18492135.

30. Kerscher M, Buntrock H. [Anti-aging creams. What really helps?] *Hautarzt.* 2011;62:607– 13. doi: 10.1007/s00105-011-2137-6.
31. Draelos ZD. The latest cosmeceutical approaches for anti-aging. *J Cosmet Dermatol.* 2007;6:2–6. DOI: 10.1111/j.1473-2165.2007.00313.x.
32. Zhai H, Behnam S, Villarama CD, Arens-Corell M, Choi MJ, Maibach HI. Evaluation of the antioxidant capacity and preventive effects of a topical emulsion and its vehicle control on the skin response to UV exposure. Skin Pharmacol Physiol. 2005 Nov-Dec;18(6):288-93. doi: 10.1159/000088014. PMID: 16145283.
33. Zhai H, Behnam S, Villarama CD, Arens-Corell M, Choi MJ, Maibach HI. Evaluation of the antioxidant capacity and preventive effects of a topical emulsion and its vehicle control on the skin response to UV exposure. Skin Pharmacol Physiol. 2005 Nov-Dec;18(6):288-93. doi: 10.1159/000088014. PMID: 16145283.
34. Kafi R, Kwak HS, Schumacher WE, Cho S, Hanft VN, Hamilton TA, et al. Improvement of naturally aged skin with vitamin A (retinol). Arch Dermatol. 2007 May;143(5):606-12. DOI: 10.1001/archderm.143.5.606;PMID: 17515510.
35. Varani J, Warner RL, Gharaee-Kermani M, Phan SH, Kang S, Chung JH, et al. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteinases and stimulates collagen accumulation in naturally aged human skin. J Invest Dermatol. 2000 Mar;114(3):480-6.DOI: 10.1046/j.1523-1747.2000.00902.x;PMID: 10692106.
36. Bhawan J. Short- and long-term histologic effects of topical tretinoin on photodamaged skin. Int J Dermatol. 1998 Apr;37(4):286-92. DOI: 10.1046/j.1365-4362.1998.00433.x; PMID: 9585903
37. Lupo MP, Cole AL. Cosmeceutical peptides. Dermatol Ther. 2007 Sep-Oct;20(5):343-9. DOI: 10.1111/j.1529-8019.2007.00148.x. PMID: 18045359.
38. Nelson BR, Majmudar G, Griffiths CE, Gillard MO, Dixon AE, Tavakkol A, et al. Clinical improvement following dermabrasion of photoaged skin correlates with synthesis of collagen I. Arch Dermatol. 1994 Sep;130(9):1136-42. DOI: 10.1001/archderm.1994.01690090060008; PMID: 8085868.
39. Ostler EL, Wallis CV, Aboalchamat B, Faragher RG. Telomerase and the cellular lifespan: implications of the aging process. J Pediatr Endocrinol Metab. 2000;13 Suppl 6:1467-76. DOI: 10.1515/jpem-2000-s621;PMID: 11202223.
40. Monheit GD, Chastain MA. Chemical peels. Facial Plast Surg Clin North Am. 2001 May;9(2):239-55, viii. PMID: 11457690.
41. Fischer TC, Perosino E, Poli F, Viera MS, Dreno B. Chemical peels in aesthetic dermatology: an update 2009. J Eur Acad Dermatol Venereol. 2010 Mar;24(3):281-92. DOI: 10.1111/j.1468-3083.2009.03409.x. PMID: 19744174.
42. Fartasch M, Teal J, Menon GK. Mode of action of glycolic acid on human stratum corneum: ultrastructural and functional evaluation of the epidermal barrier. Arch Dermatol Res. 1997 Jun;289(7):404-9. DOI: 10.1007/s004030050212; PMID: 9248619.
43. Deprez P. Textbook of Chemical Peels. Superficial, Medium, and Deep Peels in Cosmetic Practice. Informa UK, London, 2007.
44. Han SH, Kim HJ, Kim SY, Kim YC, Choi GS, Shin JH. Skin rejuvenating effects of chemical peeling: a study in photoaged hairless mice. Int J Dermatol. 2011 Sep;50(9):1075-82. DOI: 10.1111/j.13654632.2010.04712.x; PMID: 22126868.
45. Sadick NS. Update on non-ablative light therapy for rejuvenation: a review. Lasers Surg Med. 2003;32(2):120-8. DOI: 10.1002/lsm.10127; PMID: 12561045
46. Dierickx CC, Anderson RR. Visible light treatment of photoaging. Dermatol Ther. 2005 May-Jun;18(3):191-208. DOI: 10.1111/J.1529-8019.2005.05019.X;PMID: 16229721.
47. Sadick NS. Update on non-ablative light therapy for rejuvenation: a review. Lasers Surg Med. 2003;32(2):120-8. DOI: 10.1002/lsm.10127; PMID: 12561045.
48. Hardaway CA, Ross EV. Nonablative laser skin remodeling. Dermatol Clin. 2002 Jan;20(1):97-111, ix. DOI: 10.1016/S0733-8635(03)00049-4; PMID: 11859598.
49. Bjerring P, Christiansen K, Troilius A, Dierickx C. Facial photo rejuvenation using two different intense pulsed light (IPL) wavelength bands. Lasers Surg Med. 2004;34(2):120-6. DOI: 10.1002/lsm.20000;PMID: 15004823.
50. Zelickson BD, Kilmer SL, Bernstein E, Chotzen VA, Dock J, Mehregan D, et al. Pulsed dye laser therapy for sun damaged skin. Lasers Surg Med. 1999;25(3):229-36. DOI: 10.1002/(SICI)1096-9101(1999)25:3<229::AID-LSM7>3.0.CO;2-D;PMID: 10495300.
51. Prieto VG, Sadick NS, Lloreta J, Nicholson J, Shea CR. Effects of intense pulsed light on sun-damaged human skin, routine, and ultrastructural analysis. Lasers Surg Med. 2002;30(2):82-5. DOI: 10.1002/lsm.10042;PMID: 11870785.
52. Tanghetti E, Sherr E. Treatment of telangiectasia using the multi-pass technique with the extended pulse width, pulsed dye laser (Cynosure V-Star). J Cosmet Laser Ther. 2003 Jun;5(2):71-5. DOI: 10.1080/14769170310001249;PMID: 12850799.
53. Omi T, Kawana S, Sato S, Honda M. Ultrastructural changes elicited by a non-ablative wrinkle reduction laser. Lasers Surg Med. 2003;32(1):46-9. DOI: 10.1002/lsm.10119.;PMID: 12516070.
54. Hsu TS, Zelickson B, Dover JS, Kilmer S, Burns J, Hruza G, et al. Multicenter study of the safety and efficacy of a 585 nm pulsed-dye laser for the nonablative treatment of facial rhytides. Dermatol Surg. 2005 Jan;31(1):1-9.DOI: 10.1097/00042728-200501000-00001; PMID: 15720087.
55. Moody BR, McCarthy JE, Hruza GJ. Collagen remodeling after 585-nm pulsed dye laser irradiation: an ultrasonographic analysis. Dermatol Surg. 2003 Oct;29(10):997-9; discussion 999-1000. DOI: 10.1046/j.1524-4725.2003.29290.x; PMID: 12974694.
56. Bjerring P, Clement M, Heickendorff L, Lybecker H, Kiernan M. Dermal collagen production following irradiation by dye laser and broadband light source. J Cosmet Laser Ther. 2002 Jun;4(2):39-43. DOI: 10.1080/147641702320602555; PMID: 12470517.
57. Dierickx CC, Anderson RR. Visible light treatment of photoaging. Dermatol Ther. 2005 May-Jun;18(3):191-208. DOI: 10.1111/j.1529-8019.2005.05019.x; PMID: 16229721
58. Dahiya R, Lam SM, Williams EF. A systematic histologic analysis of nonablative laser therapy in a porcine model using the pulsed dye laser. Arch Facial Plast Surg. 2003 May-Jun;5(3):218-23. DOI: 10.1001/archfaci.5.3.218;PMID: 12756114.
59. Goldberg DJ, Cutler KB. Nonablative treatment of rhytids with intense pulsed light. Lasers Surg Med. 2000;26(2):196-200. DOI: 10.1002/(SICI)1096-9101(2000)26:2<196::AIDLSM10>3.0.CO;2-9; PMID: 10685092.
60. Alster TS, Garg S. Treatment of facial rhytides with a high-energy pulsed carbon dioxide laser. Plast Reconstr Surg. 1996 Oct;98(5):791-4 .DOI: 10.1097/00006534-199610000-00005;PMID: 8823015.
61. Lowe NJ, Lask G, Griffin ME, Maxwell A, Lowe P, Quilada F. Skin resurfacing with the Ultrapulse carbon dioxide laser. Observations on 100 patients. Dermatol Surg. 1995 Dec;21(12):1025-9.DOI: 10.1016/1076-0512(96)82352-1;PMID: 7496669.
62. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers Surg Med. 2004;34(5):426-38.DOI: 10.1002/lsm.20048;PMID: 15216537.
63. Hantash BM, Bedi VP, Kapadia B, Rahman Z, Jiang K, Tanner H, et al. In vivo histological evaluation of a novel ablative fractional resurfacing device. Lasers Surg Med. 2007 Feb;39(2):96-107.DOI: 10.1002/lsm.20468;PMID: 17311274.
64. Orringer JS, Kang S, Johnson TM, Karimipour DJ, Hamilton T, Hammerberg C, et al. Connective tissue remodeling induced by carbon dioxide laser resurfacing of photodamaged human skin. Arch Dermatol. 2004 Nov;140(11):1326-32. DOI: 10.1001/archderm.140.11.1326; PMID: 15545540.
65. Dierickx CC, Anderson RR. Visible light treatment of photoaging. Dermatol Ther. 2005 May-Jun;18(3):191-208. DOI: 10.1111/j.1529-8019.2005.05019.x;PMID: 16229721

66. Hardaway CA, Ross EV. Nonablative laser skin remodeling. Dermatol Clin. 2002 Jan;20(1):97-111, ix. DOI: 10.1016/S0733-8635(03)00049-4;PMID: 11859598.
67. Raulin C, Greve B, Grema H. IPL technology: a review. Lasers Surg Med. 2003;32(2):78-87. DOI: 10.1002/lsm.10145; PMID: 12561039.
68. Iorizzo M, De Padova MP, Tosti A. Biorejuvenation: theory and practice. Clin Dermatol. 2008 Mar-Apr;26(2):177-81. DOI: 10.1016/j.clindermatol.2007.09.011;PMID: 18472058.
69. Jäger C, Brenner C, Habicht J, Wallich R. Bioactive reagents used in mesotherapy for skin rejuvenation in vivo induce diverse physiological processes in human skin fibroblasts in vitro- a pilot study. Exp Dermatol. 2012 Jan;21(1):72-5. DOI: 10.1111/j.1600-0625.2011.01400.x; PMID: 22151394.
70. Eppley BL, Dadvand B. Injectable soft-tissue fillers: clinical overview. Plast Reconstr Surg. 2006 Sep 15;118(4):98e-106e. DOI: 10.1097/01.prs.0000232436.91409.30; PMID: 16980841.
71. Laurent TC, Fraser JR. Hyaluronan. FASEB J. 1992 Apr;6(7):2397-404; PMID: 1563592.
72. Sherman L, Sleeman J, Herrlich P, Ponta H. Hyaluronate receptors: key players in growth, differentiation, migration and tumor progression. Curr Opin Cell Biol. 1994 Oct;6(5):726-33. DOI: 10.1016/0955-0674(94)90100-7;PMID: 7530464.
73. Fink RM, Lengfelder E. Hyaluronic acid degradation by ascorbic acid and influence of iron. Free Radic Res Commun. 1987;3(1-5):85-92. DOI: 10.3109/10715768709069773;PMID: 3508446.
74. Carruthers A, Carruthers J. Non-animal-based hyaluronic acid fillers: scientific and technical considerations. Plast Reconstr Surg. 2007 Nov;120(6 Suppl):33S-40S. DOI:10.1097/01.prs.0000248808.75700.5f;PMID: 18090341.
75. Gold MH. Use of hyaluronic acid fillers for the treatment of the aging face. Clin Interv Aging. 2007;2(3):369-76. DOI: 10.2147/cia.s1244; PMID: 18044187.
76. Alam M, Gladstone H, Kramer EM, Murphy JP, Nouri K, Neuhaus IM, et al. ASDS guidelines of care: injectable fillers. Dermatol Surg. 2008 Jun;34 Suppl 1:S115-48. DOI: 10.1111/j.1524-4725.2008.34253.x;PMID: 18547175.
77. Eppley BL, Dadvand B. Injectable soft-tissue fillers: clinical overview. Plast Reconstr Surg. 2006 Sep 15;118(4):98e-106e. DOI: 10.1097/01.prs.0000232436.91409.30;PMID: 16980841.
78. Burgess CM, Lowe NJ. NewFill for skin augmentation: a new filler or failure. Dermatol Surg. 2006 Dec;32(12):1530-2; author reply 1532. DOI: 10.1111/j.1524-4725.2006.32369.x; PMID: 17199668.
79. Mest D. Experience with injectable poly-L-lactic acid in clinicalpractice. *Cosmetic Dermatol.* 2005;18:5–8.
80. Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. J Am Acad Dermatol. 2005 Feb;52(2):233-9. DOI: 10.1016/j.jaad.2004.08.056;PMID: 15692467.
81. Zimmermann R, Jakubietz R, Jakubietz M, Strasser E, Schlegel A, Wiltfang J, et al. Different preparation methods to obtain platelet components as a source of growth factors for local application. Transfusion. 2001 Oct;41(10):1217-24. DOI: 10.1046/j.1537-2995.2001.41101217.x;PMID: 11606819.
82. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 2004 Apr;62(4):489-96. DOI: 10.1016/j.joms.2003.12.003;PMID: 15085519.
83. Freymiller EG. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 2004 Aug;62(8):1046; author reply 1047-8.DOI: 10.1016/j.joms.2004.05.205;PMID: 15278876.
84. Kim DH, Je YJ, Kim CD, Lee YH, Seo YJ, Lee JH, et al. Can Platelet-rich Plasma Be Used for Skin Rejuvenation? Evaluation of Effects of Platelet-rich Plasma on Human Dermal Fibroblast. Ann Dermatol. 2011 Nov;23(4):424-31. DOI: 10.5021/ad.2011.23.4.424; PMID: 22148008.
85. Masaki H. Role of antioxidants in the skin: anti-aging effects. J Dermatol Sci. 2010 May;58(2):85-90. DOI: 10.1016/j.jdermsci.2010.03.003; PMID: 20399614.
86. Tanuja Y, Mishra S, Das S, Aggarwal S, Rani V. Anticedants and natural prevention of environmental toxicants induced accelerated aging of skin. *Environ Toxicol Pharmacol*. 2015;39(1):384–391. DOI: 10.1016/j.etap.2014.11.003; PMID: 25555260.
87. Chen J, Li Y, Zhu Q, Li T, Lu H, Wei N, et al. Anti-skin-aging effect of epigallocatechin gallate by regulating epidermal growth factor receptor pathway on aging mouse model induced by d-Galactose. Mech Ageing Dev. 2017 06;164:1-7. DOI: 10.1016/j.mad.2017.03.007; PMID: 28343910.
88. Bavarsad Shahripour R, Harrigan MR, Alexandrov AV. N-acetylcysteine (NAC) in neurological disorders: mechanisms of action and therapeutic opportunities. Brain Behav. 2014 Mar;4(2):108-22. DOI: 10.1002/brb3.208; PMID: 24683506.
89. Mojallal A, Lequeux C, Shipkov C, Breton P, Foyatier JL, Braye F, et al. Improvement of skin quality after fat grafting: clinical observation and an animal study. Plast Reconstr Surg. 2009 Sep;124(3):765. DOI:10.1097/PRS.0b013e3181b17b8f; PMID: 19730294.
90. Kim WS, Park BS, Kim HK, Park JS, Kim KJ, Choi JS, et al. Evidence supporting antioxidant action of adipose-derived stem cells: protection of human dermal fibroblasts from oxidative stress. J Dermatol Sci. 2008 Feb;49(2):133-42. DOI: 10.1016/j.jdermsci.2007.08.004; PMID: 17870415.
91. Bernardini FP, Gennai A, Izzo L, Zambelli A, Repaci E, Baldelli I, et al. Superficial Enhanced Fluid Fat Injection (SEFFI) to Correct Volume Defects and Skin Aging of the Face and Periocular Region. Aesthet Surg J. 2015 Jul;35(5):504-15. DOI: 10.1093/asj/sjv001; PMID: 25911629.
92. Park BS, Jang KA, Sung JH, Park JS, Kwon YH, Kim KJ, et al. Adipose-derived stem cells and their secretory factors as a promising therapy for skin aging. Dermatol Surg. 2008 Oct;34(10):1323-6. DOI: 10.1111/j.1524-4725.2008.34283.x; PMID: 18616537.
93. Derby BM, Dai H, Reichensperger J, Cox L, Harrison C, Cosenza N, et al. Adipose-derived stem cell to epithelial stem cell transdifferentiation: a mechanism to potentially improve understanding of fat grafting's impact on skin rejuvenation. Aesthet Surg J. 2014 Jan 1;34(1):142-53. DOI: 10.1177/1090820X13515700; PMID: 24334307.
94. Kafi R, Kwak HS, Schumacher WE, Cho S, Hanft VN, Hamilton TA, et al. Improvement of naturally aged skin with vitamin A (retinol). Arch Dermatol. 2007 May;143(5):606-12. DOI: 10.1001/archderm.143.5.606; PMID: 17515510.

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