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.

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. 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. Gradual loss of skin elasticity leads to the sagging phenomenon. Slowing of the epidermal turnover rate and cell cycle lengthening coincides with a slower wound healing and reduced effective desquamation in older adults. 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. 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. The overall collagen content per unit area of the skin surface is known to decline approximately 1% by year. 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. Regardless of the fact that skin aging is a biological process and but not a pathological condition, including degenerative disorders, benign and malignant neoplasms. The mainspring of any skin anti-aging therapy is to achieve a healthy, smooth, blemish-free, translucent and resilient skin. In the clinical practice it is very important to understand the patient’s wishes and to gives the satisfying results after the treatment. 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

<table>
<thead>
<tr>
<th>Cosmetological care</th>
<th>Topical medical agents or topical agents</th>
</tr>
</thead>
</table>
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

Avoiding of exogenous factors of aging, correction of life style and habits

Hormone replacement therapy

Smoking, pollution, solar UV irradiation. Stress, nutrition, diet restriction and alimentary supplementation, physical activity, control of general health.

Table 2: Intrinsic and Extrinsic factors

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

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 photaging and are considered its most important cutaneous manifestations. The strategies aimed to prevent photaging 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. Intervventional 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. Most of the anti-oxidants are categorized under vitamin C, vitamin E, carotenoids & trace elements of copper and selenium. 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.

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. 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 photaging 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. 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.

Figure 1: Molecular mechanism in skin aging.
DNA Damage

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

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 place then it becomes shorter by each division and results in limited number of cell division. Telomerase is an enzyme that promotes telomere repetitions to the end to prevent telomerases 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. UV radiation leads to excessive ROS production, which results in telomere mutations and leads to further cell death.

Inflammaging

Chronic, low-grade inflammation is also estimated as a main characteristic of the aging process. 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. 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 dermepidermis junction, on which they deposit, and macrophages are overburdened with oxidised lipids. Proinflammatory cytokines and ROS 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. 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. Nicotinamide regulates cell metabolism and regeneration, and it is used in 5% concentration as an anti-aging agent. 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.

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. Other botanicals that act as antioxidants are the isoflavones from soya.

Vitamin A or retinol and its derivates are a group of agents having antioxidative effects. Retinol is the substance that is most often used as an anti-aging compound and causes less skin irritation. It shows that retinol has positive effect on collagen metabolism. 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.

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 remodelled skin layers and sometimes spur the formation of new collagen. 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.

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:  
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.  

1. If superficial peeling targets the cornosomes, cause desquamation, lead to epidermolysis and exfoliation, increases the epidermal activity of enzymes.  
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 produce complete epidermolysis, restructure of the basal layer and restoration of the dermal architecture.  

**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. 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. 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. 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.

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. 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. Reduction of facial wrinkles by using IPL devices has shown less effect comparing to the laser technology, 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. An increase in gren zone thickness, monoclonal chondroitin sulphate and III procollagen staining as well as quantification of col-1 was measured after couple of treatments with PDL. The increase in skin collagen has also been confirmed by non-invasive ultrasonographic analysis and radioimmunoassay. Nonablative skin rejuvenation should not yet be considered an alternative for laser resurfacing. However there are interesting data showing comparative histological changes between the ablative and nonablative modalities.

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. 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 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. These devices emit light in a pixilated fashion onto the skin, producing an array of microthermal zones in the dermis. 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. Type I and type III procollagen mRNA was also elevated for atleast 6 mo.  

Monopolar RF is a non-invasive way to obtain skin tightening 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. 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. 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. 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 CO2 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 polyactic 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 improves skin thickness, collagen content, and elasticity and it enhances hydration. However, there are studies suggesting that HRT increases the risk of developing breast cancer.  

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 slow the skin aging caused by menopause, hormone replacement therapy is used to slow the skin 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


