



## Skin Ageing and its Remedies: A review

Pratibha Nand\*, Poornima Riyal  
Maharaja Surajmal Institute of Pharmacy, Delhi, India

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### ABSTRACT

**Plan:** This review mainly focus on various mechanisms and treatment strategies for skin ageing.

**Preface:** Skin ageing is a complex biological phenomenon consisting of extrinsic ageing and intrinsic ageing. The process of extrinsic ageing commonly called photoageing, involves changes in cellular biosynthetic activity which leads to gross disorganisation of the dermal matrix whereas intrinsic skin ageing of skin derived cells.

**Outcome:** The paper highlights strategies for treatment of skin ageing which causes reduction in proliferative capacity leading to cellular senescence, and altered biosynthetic activity.

**Keywords:** Skin ageing, Intrinsic, Extrinsic, Radiations, Free radicals.

### 1. INTRODUCTION

Skin is one of the most important organs of the human body as an important protective barrier between environment and internal organs but it is always constantly exposed to potentially harmful compounds and radiations<sup>1</sup> leading to skin ageing<sup>2</sup>. Skin is basically composed of epidermal and dermal layers, of which epidermis forms a barrier preventing water and heat loss and the entry of pathogenic organism while dermis is vascular. These two layers are joined together by dermal–epidermal junction (DEJ). In this the dermis is anchored to the junction by collagen VII fibrils and fibrillin-rich microfibril bundles while the epidermal keratinocytes are anchored by type IV collagen-rich basement membrane<sup>3</sup>. Dermal fibroblast are present everywhere in the skin and are responsible for synthesizing three major groups of dermal extracellular matrix (ECM) proteins<sup>4</sup>. These proteins constitute the major part of the dermis and are involved in skin ageing process.

Ageing, or senescence, means the process of getting old which is generally a natural wear and tear phenomenon and is a combination of processes of deterioration that follow the period of development of an organism<sup>5</sup>. Although each part of the body ages with the time, skin is the external organ where the sign and symptoms of aging are readily evident<sup>6</sup>. It is generally associated with increased wrinkling, sagging and laxity of skin but when considering the underlying reasons for these changes, it is important to distinguish between the effects of true biological ageing and environmental factors, such as exposure to the harmful radiations and other external agents.



For Correspondence: pratibha.msip@gmail.com

Contact: 91-8800514668

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Skin ageing can be intrinsic as well as extrinsic. Intrinsically aged skin is usually caused in sun-protected areas, while the extrinsic ageing is caused by ultraviolet radiation (UVR), smoking and other external agents<sup>7</sup>.

The most popular and ongoing approach for the treatment of skin ageing is the use of synthetic and herbal drugs having antioxidant potential, It can also be delayed by using cosmetics as well as number of pharmaceutical formulations but permeation of these exogenous agents used in treatment of skin aging, is prevented by the barrier function of skin .Therefore, the major challenge for the industry today is to provide a sufficient increase in drug penetration into skin without causing irreversible alterations to the barrier function<sup>8</sup>.Of recent, significant advances have been made which unravel the secret of the basic mechanism of aging.

## 2. Mechanism of skin ageing

Several theories are proposed for the mechanism of skin ageing, where intrinsic and extrinsic share few common mechanisms. Theories based on free radical mechanism, hormonal changes, mDNA mutation, homocysteine toxicity, reduction in hyaluronic acid (HA) are proposed till now. Though, animals and human cells have antioxidant defence system against oxidative stress, which consists of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase but insufficient levels of free radical scavenging enzymes could lead to the accumulation of superoxide anions. SODs catalyze the breakdown of the superoxide anion into oxygen and hydrogen whereas catalase catalyses the conversion of hydrogen peroxide to water and oxygen, using either iron or manganese cofactor. Glutathione peroxidase, another enzyme containing four selenium-cofactors also catalyzes the breakdown of hydrogen peroxide and organic hydro peroxides. Sometimes, this antioxidant defence system may be overwhelmed by various pathological disorders leading to production of reactive hydroxyl radicals<sup>9</sup>.

In addition to these other factors like smoking, IR radiations; anatomical variations, lifestyle etc. are also responsible for ageing. The intrinsic and extrinsic ageing processes are associated with phenotypic changes in cutaneous cells, major structural and functional changes occur in the dermal extracellular matrix (ECM) where fibrillar collagens, elastic fibres and proteoglycans are required to confer tensile strength, resilience (recoil) and hydration, respectively.

The extreme longevity of these biomolecules<sup>10</sup> compared with intracellular proteins exposes these assemblies to accumulated damage, which in turn impacts their ability to both confer mechanical properties and to mediate tissue homeostasis<sup>11</sup>. Researchers theorized that changes related to skin ageing occurs mostly in the dermis as the thickness of the dermis gets decreased and wrinkles may be formed because of the weakening of bond between the dermis and epidermis. Aged skin is marked by decreased vascularity and reduction in level of melanocytes<sup>12</sup>.

### 2.1. Free Radicals

Free Radical theory of ageing explains that reactive oxygen species (ROS) are the root cause for skin ageing both for chronological ageing and photo ageing<sup>13</sup>. With increasing age, the human antioxidative mechanisms gets deteriorated and therefore the ROS damage the cellular components more increasingly leading to the production of matrix metalloproteinases MMP-1 (interstitial collagenase), MMP-3 (stromelysin 1), and MMP-9 (gelatinase b). As a result, there is a marked elevated level of partially degraded collagen leading to cellular ageing<sup>14</sup>.

## *2.2. Hormonal levels*

Literature revealed that decreased level of sex hormones: oestrogens and progesterone in the body are responsible for the skin ageing specially the intrinsic skin ageing. The deficiency of these hormones leads to dryness, wrinkling, epidermal atrophy, collagen breakdown and loss of elasticity<sup>15</sup>.

## *2.3. Genetic material*

UVA and UVB radiations also initiate damage to the genetic material like UVA radiation causes genetic damage through generation of reactive oxygen species<sup>16</sup> which ultimately affect the up regulation of matrix metalloproteinases. Another theory suggested that as we grow old, our stem cells might lose their replicative capacity, which in turn induces ageing of skin by impaired stem cell mobilisation or reduction in number of stem cells to respond to proliferative signals. They suggested that ageing could be due to the deficiency of DNA repair mechanism and also the reduction in the ability to produce progenitors and differentiated effector cells with age<sup>17</sup>.

## *2.4. Smoking*

Tobacco smoking is another major contributing factor to premature skin ageing apart from UV-exposure, alcohol consumption skin type and gender<sup>18</sup>. Cigarette smoking promotes wrinkle formation. Like UV-exposure, nicotine also induces expression of MMPs degrading ECM in human skin. It causes decrease in capillary blood flow to the skin; it creates oxygen and nutrient scarcity in cutaneous tissue<sup>19</sup>.

## *2.5. Radiations*

UV radiation also causes a molecular chain reaction in the dermis and stimulates the production of collagenase, gelatinase and stromelysin-1 in both fibroblasts and keratinocytes which results in deterioration of both collagen and elastin components. Repeated cycles of exposure to solar radiation showed visible changes in the form of sagging skin and wrinkles<sup>20</sup>. Infrared (IR) radiation (760nm to 1mm) is divided further according to its wavelength into IRA (k = 760 nm to 1440 nm), IRB (k = 1440 nm to 3000 nm), and IRC (k = 3000 nm to 1 mm), and the depth of penetration of these radiations is inversely proportional to the wavelength. IR comprises of 54.3% of total incident solar energy where IRA similar to UV-radiation promotes ECM degradation and causes ROS formation in the mitochondria, leading to higher expression of MMP-1 and MMP-9<sup>21</sup>.

## **3. Treatment strategies**

Although ageing is a natural wear and tear phenomenon and bodily decay which is an inexorable process, it can at least be postponed or prevented by certain approaches. An effective anti-ageing compound has to play many roles because ageing is characterised by number of physiological changes. Recently, numbers of synthetic drugs and natural bioactives possessing anti-ageing properties have been reported for beneficial effects. Photoaged skin is generally characterized by irregular pigmentation, roughness, telangiectasia, fine and coarse wrinkles.

Vitamins A, E, C and procyanidins provide a photoprotective effect on photodamaged skin due to their antioxidant potential<sup>22</sup>.

Aspirin, one of the most common analgesic antipyretic drugs, was found to delay the onset of endothelial senescence by preventing reduction of NO formation/generation. It inhibited senescence-associated  $\beta$ -galactosidase activity and increased telomerase activity<sup>23</sup>. Idebenone, a benzoquinone has been reported a potent agent in the treatment of wrinkles. It has structure similarity with CoQ10 and can perform the same functions like CoQ10, but without auto oxidation process. It is more soluble than CoQ10 and acts as an antioxidant in skin ageing<sup>24</sup>.

Meclofenoxate provides anti-ageing benefits and protection against free radical damage in the brain, prevention of age related spots on the skin, improved memory and learning ability<sup>5</sup>. Metformin is an antidiabetic drug, but was found effective in age-related damage. Though it works through enhancing the sensitivity of cell surface insulin receptors of muscle and fat cells to insulin involved in gluconeogenesis in the liver and thus reduce the risk of glycation<sup>25</sup>.

The thickness of skin decreases with age and the loss is observed dermis, epidermis, cells and extracellular matrix. Percutaneous application of an L-fucose-containing preparation produced an increase of skin thickness and a densification of collagen bundles as it could influence collagen biosynthesis and accumulation by fibroblasts. Results indicated that L-fucose penetrated relatively rapidly in the deeper layers of the dermis and profound effect on dermal thickness and collagen bundle density and packaging was observed<sup>26</sup>.

It has been reported that Carnosine (balanyl- L-histidine), a naturally occurring compound, found in various tissues like skeletal muscles, myocardium and brain, with well-studied clinical benefits. Recently, carnosine has been used for improving athletic endurance, as a skin protecting/wrinkle preventing agent including wound management, as a biomarker in nutrition and a general anti-ageing supplement. It has the capability of scavenging reactive oxygen species (ROS) and products of lipid peroxidation<sup>27</sup>.

Another traditional oriental medicine *Panax ginseng* containing protein, fats and ginsenosides, major bioactive component having an aglycone was investigated for anti-wrinkle effects. Dietary supplementation with red ginseng extract for 5 weeks significantly inhibited wrinkle formation caused by chronic UVB irradiation. Results suggested that the mechanism underlying the anti-wrinkle effects of Korean red ginseng in UVB-exposed hairless mice involves the inhibition of collagen degradation rather than increased collagen synthesis<sup>28</sup>.

Soy has been used as Chinese medicine for thousands of years for its health and nutritional values, and for skin care purpose. Advanced skin care research has shown that soy isoflavone and genistein are effective in reducing damage to the skin from the sun. In a study, it was found that isoflavone extract as functional cosmeceutical candidate from soybean cake as it attenuated UVB-induced keratinocyte death. The in vitro effects and possible mechanisms of soybean extract on UVB protection were determined in HaCaT cells. In vitro studies showed that UVB-induced HaCaT cell death and the phosphorylation decreased in the presence of isoflavone extract. Furthermore, topical application of isoflavone extract before UVB irritation decreased the epidermal thickness and the expressions of COX-2<sup>29</sup>.

Lycopene is present in tomatoes and has been reported to be capable of directly blocking ultraviolet rays causing damaging effect on skin<sup>30</sup>. Another study revealed the beneficial effects of resveratrol, a phytoalexin present in a number of plants. This polyphenol is also present in red wine and through its antioxidant, anti-proliferative properties, provides protection against age-related macular degeneration<sup>31</sup>.

Hence, to deal with aging effectively, many drugs, nutritional supplements and food products can be developed to slow, stop or reverse the aging process.

#### 4. CONCLUSION

In this paper existing interventions that reviewed suggest that more rigorous scientific studies are needed to formulate a product so that the natural wear and tear of ageing can be postponed. It seems likely that a development of new drug with more efficacies based on the physiological changes in the structure of skin will give better insight into the regulation of ageing process.

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