Seanol Science Center Review

SEANOLOGY

Skin Elasticity and Sea Polyphenols

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Skin elasticity is a hallmark of young and healthy skin. However, it declines over time and allows wrinkle formation and slackness of the skin. Topical applications of sea polyphenols extracted from *Ecklonia cava* have long been claimed to remarkably improve skin elasticity in numerous anecdotal trials. This review attempts to understand the scientific mechanisms underlying such effect by analyzing the reported study results on sea polyphenols pertaining to the factors that affect skin elasticity.

Keywords: *elasticity, elastin, collagen, hyaluronic acid, Ecklonia cava*

Introduction

With the increase in life expectancy, a growing number of elderly individuals desire to preserve a youthful and attractive appearance. Skin elasticity is a crucial feature of young and healthy skin. It is because the deficiency of this quality leads to sagging of the skin as well as wrinkle formation as evidently noticed in aged skin. The loss of skin elasticity progresses over the entire life span. The leaves of brown alga *Ecklonia cava* have traditionally been used to heal sun-burn skins of female divers of Jeju Island, South Korea. During the past decade, topical use of the sea polyphenols extracted from *Ecklonia cava* have been claimed to remarkably improve skin elasticity. This review attempts to understand the scientific mechanism underlying such claimed benefits by analyzing the biological properties of sea polyphenols pertaining to the parameters involved in skin elasticity.

Determinants of Skin Elasticity

The driving force for the elastic property of the skin is a coil-like protein called “elastin” which forms a resilient rubbery network in the dermis together with other matrix components such as collagen and proteoglycan. The fundamental scaffold of the skin that provides a firm ground for the formation of elastin network is made of collagen fiber. On the other hand, the soft texture and volume of the skin that give an elastic look is enabled by the water-holding power of proteoglycan. Thanks to the strength of collagen fiber and the water-holding capacity of proteoglycan in the dermis, the skin can be both strong and flexible with proper volume, which contributes to skin elasticity. Together with these two basic skin matrix components, the elastin network which interweaves these components enables the skin to retain its proper shape after being deformed by the mechanical forces such as gravity or shear forces. Elastin network provides the skin elasticity by rubber-like molecular motion. Since an elastin molecule prefers a coil form to a stretched one, it is restored to the original coil shape after being temporarily stretched by an external force (Figure 1). Cross-links between elastin molecules extend this local molecular property to a tissue level (elastic fiber network in the dermis). Fully functional elastin network in young and healthy skin can completely and quickly return to the original shape and provides the mechanical motif of resilience and elasticity to the skin tissue. Therefore, both the integrity of individual elastin molecules and the proper location of the cross-links between elastin molecules affect the elastic characteristic of the skin tissue.

Overall, the skin elasticity depends on the proper

organization and integrity of the three components as summarized below:

- Mechanical resilience of dermis provided by elastic property of elastin network (like elastic rubber)
- Tough and strong scaffold of dermis provided by collagen fiber (like tough leather)
- Proper volume, softness and flexibility of dermis realized by water-holding power of proteoglycan (like diaper)

Risk Factors to Skin elasticity

Most researchers agree that skin elasticity decreases with age. The study performed by Pierard *et al* (1998) showed the evidence of a time-related reduction of elasticity and increase of extensibility in facial skin. The combination of increased extensibility and reduced elasticity is translated into skin slackness present in the aged skin (Figure 2).

Loss of skin elasticity is induced by several environmental stimuli combined with natural aging process (Table 1, Figure 3). Among environmental stimuli, UV light from the sun is the most dangerous because it damages DNA molecules and amplifies the production of ROS. Our body is substantially equipped with anti-oxidant defense system including SOD, catalase, glutathione, and glutathione peroxidase to protect from endogenously generated ROS during our natural respiration process. However, since the activity of the defense system declines year by year, the uncontrolled ROS (oxidative stress) from respiration and/or environment is gradually elevated and causes loss of skin homeostasis as one gets older. The oxidative stress itself modifies protein and gene, and leads to abnormal protein synthesis. At the same time, the accumulation of DNA damage leads to mutation and synthesis of abnormal proteins. Furthermore, the increased ROS by UV irradiation combined with aging stimulates several signal transduction and increases inappropriate gene activity. Notably, several proteinases such as matrix metalloproteinases, elastase and hyaluronidases are overly expressed to break down matrix proteins such as collagen, elastin and hyaluronic acid. These events positively feedback to each other and forms a vicious cycle toward the loss of skin homeostasis including loss of skin elasticity.

Table 1. Biological Components Essential for Skin Elasticity

Component	Function
Collagen	Forms a tough fiber network to provide the tensile strength to the skin.
Elastin	Forms a rubber-like fiber network interlaced between collagen fibers to give the skin the ability to return to its original shape after being stretched.
Proteoglycan	A major water-holding component of the dermal matrix made of branches of glycoproteins and a backbone of hyaluronic acid.
Hyaluronic acid	Forms the backbone of the proteoglycan structure. Its degradation results in the loss of water-holding power and elicits inflammation.
Matrix proteins	A collective term for proteins such as collagen, elastin and proteoglycans which are essential for the dermal structure and mechanical properties.
Fibroblast	A type of cell that synthesizes the extracellular matrix and collagen in various tissues including dermis
Peripheral blood circulation	It is essential for dermal cells to be healthy and fully functional. Dermal fibroblasts that synthesize matrix proteins solely depend on blood supply through small blood vessels existing in the dermis.
Dermis	A layer of skin between the epidermis and subcutaneous tissues. Major structural components of the dermis are collagen, elastic fibers, and proteoglycans.

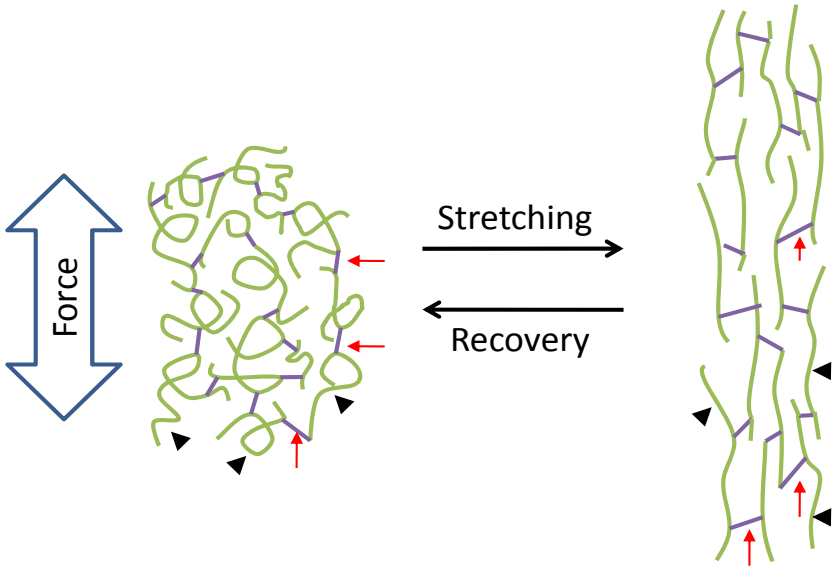


Figure 1. Morphological change of elastin fiber network. Left: Relaxed state of elastin network. Right: Stretched elastin network. Arrow heads: Single elastin molecules. Arrows: Cross-links between elastin molecules.

The overall process toward loss of skin elasticity is perpetuated by chronic inflammation which is orchestrated by transcription factors NF-kB and AP-1. AGE is produced by reaction between proteins and sugar molecules and provokes degeneration process of our body. AGE is naturally accumulated upon aging and its production is accelerated under high blood sugar level. More specifically in the dermis, AGE leads to abnormal cross-linking of matrix proteins in the dermis and compromise the mechanical properties of skin.

Under chronic inflammation, peripheral circulation is compromised to suppress cell growth, accelerating the degenerative modification of skin matrix. Altogether, in the aging skin, undersupply of fully functional matrix proteins together with oversupply of incomplete or damaged matrix proteins leads to gradual loss of dermal elasticity, which is characterized by:

- Decreased elastic recovery of elastin network due to increased disorder in the network structure
- Loss of isotropic (omnidirectional) alignment of collagen scaffolding
- Loss of water in the dermis

Scientific Factors of Sea polyphenols Beneficial to Skin Elasticity

A body of valuable scientific studies on various levels of molecular biology related with skin elasticity has been reported on sea polyphenols (Figure 4). Overall, those studies reveal that sea polyphenols are capable of multi-factorial intervention throughout the cascade of events involved in the decline of skin elasticity (Table 3).

Hwang *et al* (2005, 2006) demonstrated for the first time the protective effect of sea polyphenols from UV rays. They discovered that a topical or oral administration of a sea polyphenol complex (6,6'-bieckol, 7-phloroeckol, dieckol, eckol, 8,8'-dieckol, phlorofucofuroeckol) from *Ecklonia cava* prevented skin carcinogenesis in the hairless mice exposed to UVB for 24-weeks. They also found that its cancer preventive effect was accompanied by a remarkable down-regulation of inflammatory enzymes such as COX-2 and iNOS which were amplified during chronic exposure to UVB on the skin. This study clearly demonstrated that sea polyphenols protect skin cells from UVB-induced mutation and prevents chronic inflammation.

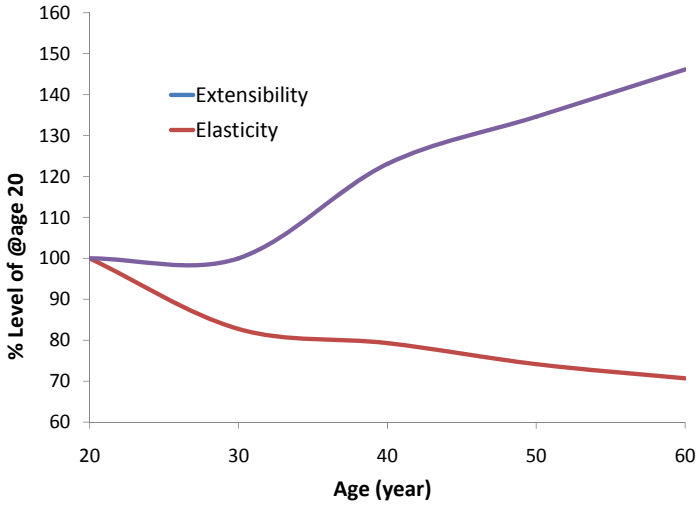


Figure 2. Time-dependent change of elasticity and extensibility of facial skin in women (Pierard *et al*, 1998). Extensibility increases and elasticity decreases along time.

Heo *et al* (2009) reported some possible mechanisms for such protective activity of sea polyphenols from UVB. They evaluated oxidative stress, DNA damage and morphological changes in human skin cells in the absence and presence of sea polyphenols. They found that the addition of eckol and dieckol to human fibroblast reduced intracellular ROS and increased cell viability under UVB irradiation. Moreover, dieckol showed strong protective effect against UVB-induced DNA damage and morphological changes. Such studies by Hwang *et al* (2006) and Heo *et al* (2009) unequivocally indicate that sea polyphenols prevent loss of skin homeostasis by effectively reducing the upstream risk factors including DNA damage, oxidative stress and inflammation induced by UV light.

As one ages, one's antioxidant defense capacity declines to allow the oxidative stress accumulate in skin cells. It triggers the cascade of events toward the loss of skin elasticity independently from or in combination with UV-induced events. Many studies demonstrate that sea polyphenols are not only potent ROS scavengers but also boosters of cellular antioxidant defense capacity.

Li *et al* (2009) and Ahn *et al* (2007) showed that individual sea polyphenols from *Ecklonia cava* such as eckol, dieckol, 7-phloroeckol, phlorofucofuroeckol A, 6,6'-bieckol and fucodphloroethol G possess potent antioxidant activities in diverse assay systems including a hydrophobic system (linoleic acid), ESR-based radical measurement (DPPH, hydroxyl, superoxide, peroxyl radicals), intracellular ROS measurement, cellular membrane protein oxidation and intracellular glutathione level and myelo-peroxidase activity.

Kim *et al* (2009) and Kang *et al* (2007) discovered that eckol and triphlorethol are capable of boosting the cellular antioxidant defense capacity. These findings indicate that sea polyphenols can minimize the oxidative stress by a synergy created by elimination of ROS and by enhancement of the antioxidant defense capacity.

Overall, by reducing important upstream risk factors such as DNA damage, oxidative stress and inflammation, sea polyphenols can effectively contribute to the recovery of natural healing mechanism (or homeostasis) of skin, and consequently to the prevention of the downstream events that physically damage dermal matrix structure.

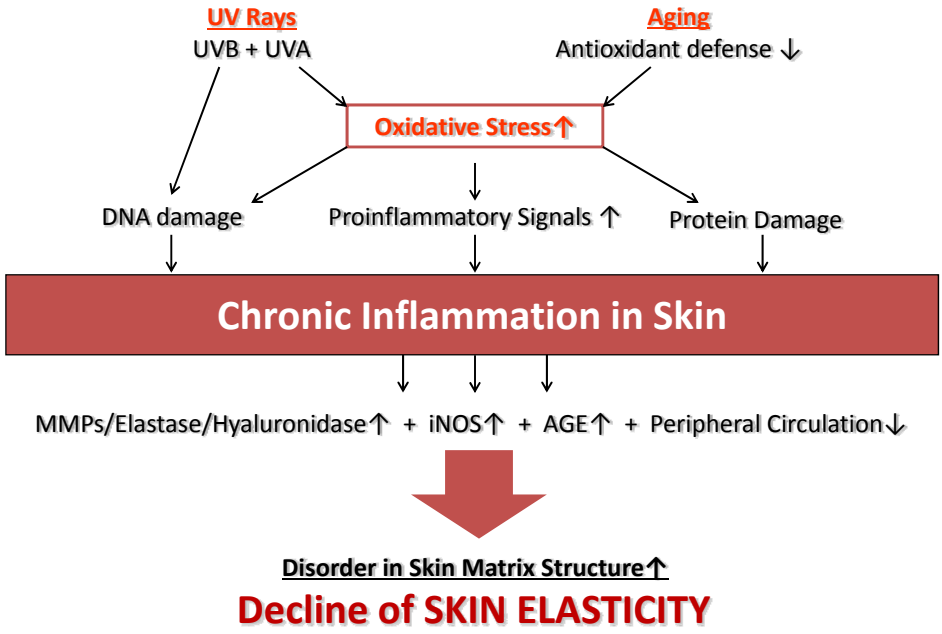


Figure 3. Cascade of risk factors leading to decline of skin elasticity. In the upstream of the cascade, combination of UV rays and the decline of intrinsic antioxidant defense capacity leads to DNA damage and increase in oxidative stress, which in turn elevate the level of proinflammatory signals and modified proteins. These upstream events, separately or in combinations, provoke chronic inflammation of skin. Under chronic inflammation, production of matrix proteins is slowed down and their destruction is accelerated due to compromised peripheral circulation and amplification of downstream risk factors such as matrix degrading enzymes, iNOS and AGE. Such combination of downstream risk factors leads to gradual loss of integrity of skin matrix structure which is translated into decline of skin elasticity.

On the other hand, down-stream risk factors that are involved in over-paced breakdown or abnormal cross-linking of matrix proteins damage skin elasticity by physically destroying the integrity of skin matrix.

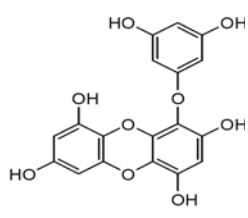
As a mechanical motif for skin elasticity, elastin network in the dermis is crucial to elastic recovery of skin from gravity or other mechanical forces. However, under chronic inflammation and/or oxidative stress, an enzyme called “elastase” which hydrolyzes elastin in the dermis is over-activated to excessively break down elastin fibers, leading to loss of dermal elasticity. Bu *et al* (2006) found that sea polyphenols including eckol, phlorotannin A, triphlorethol, dieckol and phlorofucofuroeckol A isolated from *Ecklonia cava* have potent inhibitory activities against elastase.

As a strong mechanical support underlying skin elasticity, the integrity of collagen fibers in the dermal matrix is of fundamental importance. Kim *et al* (2006) found that a sea polyphenol extract from *Ecklonia cava* inhibits the activities of MMPs (MMP-1, 2 and 9) which degrades collagen fibers. Joe *et al* (2006) further showed that individual sea polyphenols such as eckol and dieckol also inhibit MMP-1 expression in human dermal fibroblasts under an inflammatory condition. They also showed that this activity was correlated with a decreased expression of key genes (AP-1 and NF-kB) required for the full activation of MMP-1. Most recently, Saeki *et al* (2009) confirmed the overall protective effect of sea polyphenols from UV rays by showing that a sea polyphenol preparation from *Ecklonia cava* inhibits both the activity and expression of MMPs (MMP-1, 2 and 9) induced by UVA and UVB irradiation in human skin cells. These findings indicate that sea polyphenols work at multiple biological levels, and are able to regulate both upstream and downstream risk factors that contribute to decline of skin elasticity.

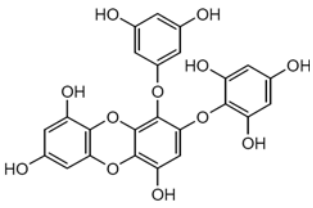
Table 2. Risk factors of Skin Elasticity

Factor	Sources and Consequences
UVA	315~400nm of radiation which penetrates into dermis and indirectly causes DNA damage and chronic inflammation via generation of free radicals.
UVB	280~315nm of radiation causing sunburn, directly damaging DNA in the epidermis. Prolonged exposure to it causes skin cancer. Also indirectly causes DNA mutation and chronic inflammation via generation of oxidative stress.
ROS (Reactive Oxygen Species)	A collective term representing various types of oxygen free radicals such as superoxide, hydroxyl, alkoxy, hydrogen peroxide, lipid peroxide, etc.
DNA damage	Caused by UVB or shorter wavelength radiation or by oxidative stress. Excess or repeated occasion causes inflammation and skin cancer.
Protein modification	Caused by oxidation or glycation of proteins; compromises the functional and structural integrity of skin matrix and provoke inflammation and aging
Proinflammatory signals	Signal molecules that alarm the emergency state of a local tissue to the immune cells in surveillance. Promotes inflammation.
Chronic inflammation	A persisting low-level inflammation. Induced and perpetuated by NF-kB and/or AP-1 that activates a body of inflammatory genes. Suppresses production and promotes degradation of matrix proteins.
MMPs (Matrix Metalloproteinases)	Degrades matrix proteins. In the skin, MMP-1, 2 and 9 are activated by UV rays, oxidative stress or proinflammatory signal to degrade collagen type I, IV and VII, respectively.
Elastase	Degrades elastin. Activated by chronic inflammation.
Hyaluronidase	Degrades hyaluronic acid. Activated by chronic inflammation.
Inflammatory enzymes	Enzymes such as COX-2 or iNOS which are induced at sites of inflammation and cause various inflammatory symptoms.
AGE (Advanced Glycation End-product)	Caused by abnormal glycation of proteins. Provoke inflammation and accelerate aging. Its formation is accelerated under hyperglycemia.
Compromised peripheral circulation	Under chronic inflammation or in aging, it is limited due to insufficient dilation of blood vessels and/or high blood thickness. Limits normal blood supply to cells.

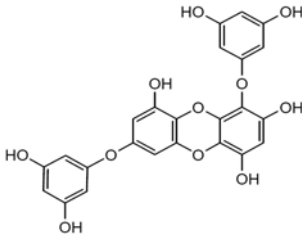
The integrity of hyaluronic acid inside the dermal matrix is also important in overall skin elasticity because hyaluronic acid form the core of the proteoglycan which enables skin to maintain its proper volume and flexibility by holding large amount of water (>90%) in the dermis. However, under chronic inflammation and/or oxidative stress, a hydrolyzing enzyme called “hyaluronidase” is over-activated and excessively breaks down hyaluronic acid. This event leads to the destruction of the proteoglycan network and the consequent reduction of the water-holding capacity of the dermis, contributing to an aged appearance of one’s skin. The excessive break-down of hyaluronic acid also provokes allergic symptoms leading to dysregulation of homeostasis of skin which aggravates the decline of skin elasticity. Bu *et al* (2006) found that sea polyphenols (eckol, phlorotannin A, triphloroethol, dieckol and phlorofucofuroeckol A) isolated from *Ecklonia cava* are potent inhibitors of hyaluronidase.



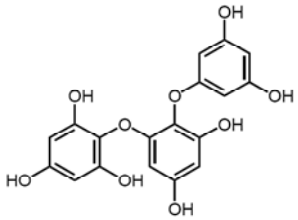
Eckol



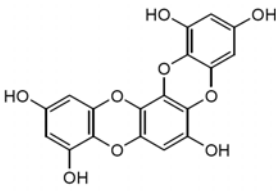
2-Phloroeckol



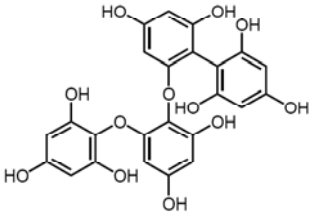
7-Phloroeckol



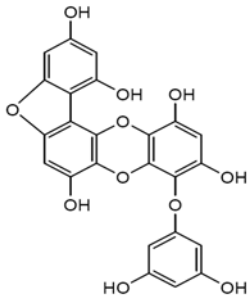
Triphloroethol A



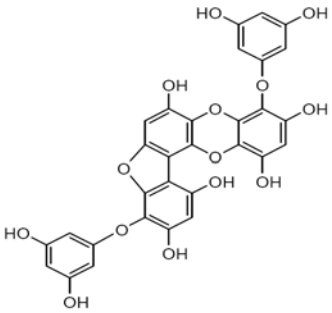
Phlorotannin A



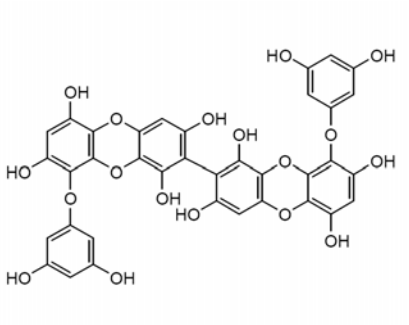
Fucodiphloroethol G



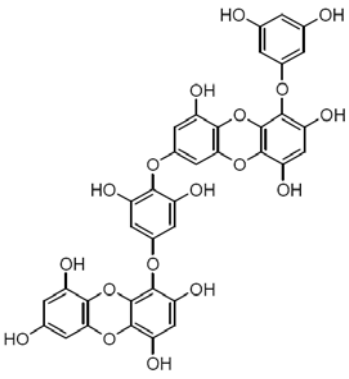
Fucofuroeckol A



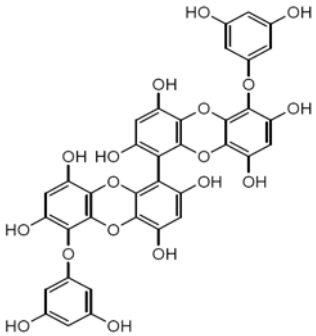
Phlorofucofuroeckol A



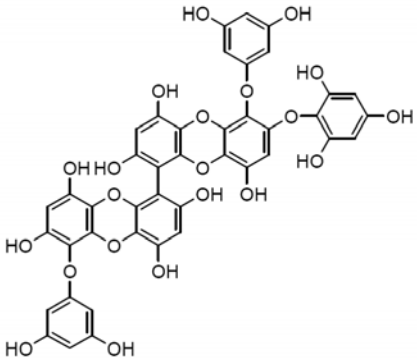
8,8’-Bieckol



Dieckol



6,6’-Bieckol



2-O-(2,4,6-trihydroxyphenyl)-
6,6’-bieckol

Figure 4. Chemical structures of sea polyphenols of Ecklonia cava with potent protective effects for skin elasticity.

The aging skin is also characterized by the increase in abnormal cross-linking of the matrix proteins in the dermis. Proper cross-linking of the matrix proteins such as elastin and collagen is crucial to healthy and resilient network structure of skin matrix. However, misplaced cross-links due to ROS and AGE deteriorate the mechanical property of the skin. Potent antioxidant and anti-AGE activities of sea polyphenols can contribute to the elimination of such risk factors. In addition to numerous studies on the antioxidant effects of sea polyphenol, Okada *et al* (2004) found potent anti-AGE effect in 7-Phloroeckol, eckol and dieckol.

Chronic inflammatory state of the skin accompanies compromised peripheral circulation in the dermis, which causes deficiency of cellular necessities such as oxygen, nutrients and hormones in the dermal cells. This situation contributes to faster loss of matrix proteins essential for proper elasticity of skin. Under chronic inflammation, peripheral blood vessels tend to overly contract, and the blood thickness tends to be abnormally high. The combination of these two factors limits sufficient blood circulation in the dermal tissue. Based on numerous studies on the potent antioxidant and anti-inflammatory effects, sea polyphenols are believed to counteract such factors and improve peripheral circulation in the dermis. In addition to such indirect upstream contribution, Hong *et al* (2006) found that sea polyphenols from Ecklonia cava can help blood vessels to relax. Studies by Jung *et al* (2006) and Nagai *et al* (2006) support this effect by showing their inhibitory activity against ACE (angiotensin converting enzyme) which is over-activated to resist relaxation (dilation) of blood vessels under chronic inflammation. Furthermore, Fukuyama *et al* (1985, 1989a, 1989b, 1990) and Nakayama *et al* (1989) discovered that sea polyphenols are able to optimize the blood thickness by regulating the balance of anti-plasmin and plasmin activity.

Finally, the non-toxic nature of sea polyphenols can never be overemphasized. In numerous cytotoxic studies, sea polyphenols show unprecedentedly low toxicity as compared with other natural antioxidant compounds. Non toxicity at or beyond 100μg/mL in various types of cells (Kim *et al*, 2006) together with potent anti-aging activities is the hallmark of sea polyphenols that enables effective protection from the loss of skin elasticity and even healing of aged skin.

Table 3. Molecular biological factors of sea polyphenols in support of skin elasticity

Factor	References
Protection from UVB	Hwang *et al*, 2005, 2006; Heo *et al*, 2009
Protection from UVA	Saeki *et al*, 2009
DNA protection	Heo *et al*, 2009
Enhancement of Cellular Antioxidant Defense	Kim *et al*, 2009; Kang *et al*, 2007
Protection from ROS	Li *et al*, 2009; Ahn *et al*, 2007; Shin *et al*, 2006; Kang *et al*, 2003
Inhibition of AGE formation	Okada *et al*, 2004
Inhibition of Protein Damage	Li *et al*, 2009
Suppression of Chronic Inflammation	Hwang *et al*, 2005, 2006; Joe *et al*, 2006
Inhibition of MMPs	Saeki *et al*, 2009; Kim *et al*, 2006; Joe *et al*, 2006
Inhibition of Elastase	Bu *et al*, 2006
Inhibition of Hyaluronidase	Bu *et al*, 2006
Down-regulation of inflammatory enzymes	Hwang *et al*, 2005, 2006
Facilitation of peripheral circulation	Hong *et al*, 2006; Jung *et al*, 2006; Nagai *et al*, 2006; Fukuyama *et al*,1985, 1989a, 1989b, 1990; Nakayama *et al*, 1989

Conclusion

Skin elasticity is a representative quality of the young and beautiful skin. In this review, determining factors for skin elasticity, its risk factors and molecular biological factors of sea polyphenols that can beneficially contribute to it have been reviewed. Compared with polyphenols originated from land, sea polyphenols were introduced to the scientific community very recently. However, based on the available studies on sea polyphenols, this group of natural chemicals shows intriguing sets of properties related with skin health and beauty (Table 3). Their impressive non-toxicity together with their potent antioxidant, anti-inflammatory and pro-circulatory activity puts these chemicals on an extraordinarily advantageous position in various cosmetic applications.

About the author

Dr. Hye Jeong Hwang has been working on chemistry and molecular biology of sea polyphenols for over ten years. She demonstrated the protective effect of sea polyphenols from chronic UVB irradiation in *in vivo* system for the first time in collaboration with Dr. GD Stoner in James Cancer Center, Ohio State University.
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