Cloud Publications
International Journal of Advanced Nutritional and Health Science
2014, Volume 2, Issue 1, pp. 67-88, Article ID Med-164
ISSN 2348-5140

Cloud Publications

Review Article | Open Access

Botanical Antioxidants for Skin Health in the World of Cosmeceuticals

Andreea Simo[1], Naiome Kawal[1], Gopinadhan Paliyath[2] and Marica Bakovic[1]

[1]Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, ON N1G 2W1, Canada
[2]Department of Plant Agriculture, University of Guelph, Guelph, ON N1G 2W1, Canada

Correspondence should be addressed to Marica Bakovic, mbakovic@uoguelph.ca

Publication Date: 29 August 2014

Article Link: http://medical.cloud-journals.com/index.php/IJANHS/article/view/Med-164

Abstract The desire to maintain a youthful appearance in an aging population has accelerated several advancements in the cosmeceuticals market. The term cosmeceutical defines products containing bioactive substances that cannot be considered cosmetics or drugs. A variety of ingredients have been used in cosmeceuticals to improve the health and appearance of aged skin, and during the past decade, the utility of botanical natural products have gained much attention in the West. Throughout this review, the skin aging, and photoaging are discussed, mechanisms which underlie these processes are explored, and treatment options using natural plant extracts are examined.

Keywords *Skin Aging; Dermatology; Antioxidants; UV Rays; Cosmetics*

1. Introduction

Improved life conditions as well as medical and technological developments have led to an increase in life expectancy, with a higher number of people now living to a comparatively longer life, with the elderly population becoming a significantly higher proportion of the population in many countries (Giacomoni, 2005). Biologists and the pharmaceutical industry are seeking ways to achieve more success in improving the quality of life in the elderly. Some believe that it is possible to extend the lifespan of humans and therefore seek ways to increase longevity; while others have more reserved expectations and focus on applications that make it possible to grow older while avoiding aging and its associated pathologies. As a result, aging and longevity are considered as two different fields of research by most scientists (Giacomoni, 2005). A commonly accepted definition of aging is the accumulation of molecular damage with time (Giacomoni, 1992). Research employing this model definition has been able to make several advances in understanding the mechanisms of skin aging, given the easy access to skin tissues. Various research approaches use models such as cell cultures, animal research and human studies, thus facilitating the search for effective rejuvenating treatments (Giacomoni, 2005). Together with the aging of muscular and skeletal systems, skin aging is a process with very direct effects. The skin is a major sensory organ, as it is the body's first line of defence

against infectious organisms and physical harm, and it plays a critical role in controlling body temperature. While slowing the aging processes of the skin will not only help maintain a youthful appearance, but it will also have beneficial effects for the whole body. The skin is an ideal model for studying the onset of aging because it is the easiest organ to observe, and aging of the skin is not a life-threatening process (Giacomoni, 2005).

2. Inflammatory Models for Skin Aging

Collecting knowledge about the skin aging process has led to the micro-inflammatory model, which describes how both internal and external factors can contribute to the process (Giacomoni, 1996a, 2001, 2005). This model focuses on observations indicating that the majority of factors identified to speed up skin aging share common features, such as the ability to initiate the synthesis of intercellular adhesion molecule-1 (ICAM-1) in endothelial cells. Factors known to speed up the aging process include ultraviolet (UV) radiation, trauma, and hormonal imbalance, among several others (Giacomoni, 2005). After synthesis, ICAM-1 is transported to the surface of the endothelial cells in the capillary vessels of the dermis, where it signals monocytes and macrophages to attach to the surface of capillary vessels and migrate into the dermis.

These steps are controlled by the release of pro-oxidants and by hydrolytics enzyme activation which damage the extracellular matrix and surrounding cells (Giacomoni, 1996b). The cell damage triggers an arachidonic -acid dependent inflammatory response to release prostaglandins and leukotrienes which signal the mastocytes to release histamine and tumour necrosis factor 1 alpha (TNF-1α). Histamine and TNF-1α can further induce more endothelial cells of the skin capillaries to synthesize ICAM-1 and to bind circulating monocytes and macrophages. Numerous experiments provide research that this self-maintaining and self-amplifying micro-inflammatory is believed to be responsible for skin damage via production of highly reactive oxygen species (ROS), ultimately resulting in skin aging.

This model focuses on the importance of identifying major environmental and lifestyle factors which cause skin aging and avoid them. The sun is still the greatest environmental factor that accelerates skin aging. Many defences are available against solar radiation, including a number of natural and synthetic sunscreens with varying SPF. Sunscreens are photostable, non-irritant and non-phototoxic substances which are able to absorb UV radiation before it can cause cellular damage (Giacomoni, 2005).

3. Skin Aging Process: Intrinsic Aging and Extrinsic Aging

Several changes commonly linked with skin aging are a direct result of sun exposure. During the 19th century, researchers observed differences in the facial skin of outdoor workers when compared to that of indoor workers (Nghiem et al., 2001). The skin of these outdoor workers had several changes associated with various skin cancers, such as thickening and brownish discoloration on light-exposed skin (Nghiem et al., 2001). The skin aging process falls into two categories: natural skin aging (intrinsic aging) and photoaging (extrinsic aging). Intrinsic aging is induced by internal physiological factors, while extrinsic aging results from exposure to various external factors (Thring et al., 2009).

3.1. Intrinsic Skin Aging

Intrinsic aging is characterized by reduced collagen synthesis, degeneration of elastic fiber networks, and loss of hydration, resulting in laxity, fine wrinkling and the development of benign growths (Criscan et al., 2012). This process occurs as slow but progressive and irreversible tissue degeneration. Telomere shortening and metabolic oxidative damage from ROS play a key role in the process of aging (Kosmadaki et al., 2004). In aged skin, there is elevation of transcription factor

activator protein 1 (AP-1) (Chung et al., 2000), which is involved in cellular processes such as differentiation, proliferation, and apoptosis (Ameyar et al., 2003). AP-1 is also involved in promoting collagen breakdown by upregulating matrix metalloproteinases (MMPs) (Helfrich et al., 2008).

MMPs contribute to remodeling of tissue associated with several physiological and pathological processes including morphogenesis, tissue repair and cirrhosis (Helfrich et al., 2008). The activity of MMPs is elevated in aged skin, and is associated with increased levels of degraded collagen (4-fold higher in aged vs. young individuals) (Fisher et al., 2002). Furthermore, synthesis of types I and III procollagen is reduced in aged skin the combination of increased collagen breakdown and decreased synthesis of new collagen results in an overall decrease in collagen levels (Kim et al., 2004; Varani et al., 2000).

3.2. Extrinsic Skin Aging

Extrinsic photoaging is characterized by wrinkling and furrowing with a thickening of the skin, along with a variety of benign, premalignant, and malignant neoplasms (Gilchrest, 1989). UV irradiation from the sun leads to the generation of ROS which results in the upregulation of AP-1 and downregulation of transforming growth factor β (TGF-β). An increase in AP-1 activity leads to the augmentation of MMPs which would subsequently trigger the breakdown of collagen.

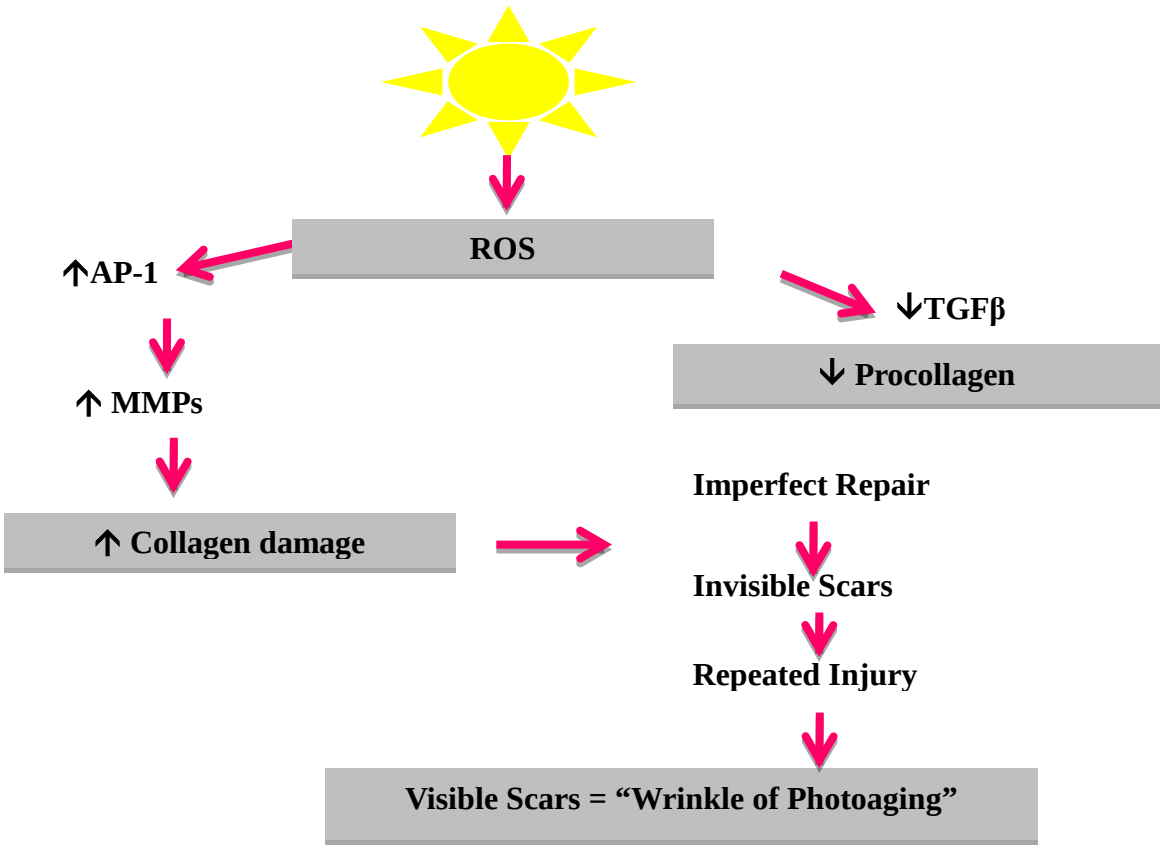

Figure 1: *The Effects of UV Rays from the Sun in the Process of Photoaging Indicating where Botanicals can Mediate Positive Changes, to Prevent and/or Decrease Signs on Photoaging*

As a down regulation in TGF-β activity is associated with a decrease in procollagen production, together an increase in collagen breakdown combined with a decrease in procollagen production results in repeated exposure to UV irradiation. This repeated exposure leads to the accumulation of damage, and eventually results in visible solar exposure scars or wrinkles associated with Photoaging

(see Figure 1) (adopted from Helfrich et al., 2008). Histologically, when compared to sun-protected skin, a 20% reduction in total collagen and a decrease in cellular content were observed in photo-damaged skin (Schwartz et al., 1993). The molecular changes of photoaging are considered to amplify natural skin aging (Fisher et al., 2002). As a result, UV radiation suppresses cell-mediated immunity, and predisposes individuals to skin cancer, immune system failure, and infection. Furthermore, UV radiation induces suppression of the local effector mechanisms involved in immune responses to recall antigens and inhibits the contact hypersensitivity response (Cooper et al., 1992; 1995; Damian et al., 1997; Morison et al., 1985; Yoshikawa et al., 1990). Such exposure causes alterations in the connective tissue through the formation of lipid peroxides, cell contents and enzymes, as well as ROS (Thring et al., 2009). ROS are free radicals, defined as atoms or molecules with an unpaired electron; and it is this electron that causes much of the damage (Giacomoni et al., 1992). Lipid peroxides can be broken down to secondary products that damage the extracellular matrix, while ROS are associated with the loss of skin elasticity (Benaiges et al., 1995; Kaur et al., 2006). Biological systems require ROS for various metabolic pathways, thus the body is able to generate reactive oxygen species such as superoxide and nitric oxide through defined pathways (Han et al., 2001; Lupo et al., 2007). However, overproduction ROS can cause severe oxidative stress and thus damage tissues, through inactivation and degradation of protein, lipid, carbohydrate and cellular DNA components (Brooker, 2011). In addition to nuclear DNA, mitochondrial DNA can also be transformed by oxidative stress. As DNA repair is less efficient in mitochondria, mutations rapidly accumulate. A common deletion in the DNA has been identified and shown to be very common in photoaged cells; this deletion can be generated by UVA and such mutations may alter the ability of cells to carry out oxidative phosphorylation, ultimately generating additional oxidative stress (Pinnell et al., 2003).

4. UV Rays and Skin Cancers

The foundation of photoaging therapy consists of a broad spectrum ultraviolet-A radiation (UVA) and ultraviolet-B radiation (UVB) sunscreens. UVR causes several acute effects in the skin, including immediate pigment darkening, delayed tanning, sunburn, epidermal thickening, as well as several immune responses. Most importantly, UVA and UVB radiation have been observed to contribute to the disruption of extracellular matrix, which is a characteristic symptom of photoaging (Sorg et al., 2005; Talwar et al., 1995). It has long been thought that UVB causes most damage, but it is becoming increasingly evident that the biological effects of UVA is significantly more important; UVA also penetrates the skin more deeply than does UVB (Dekker et al., 2005). The mechanism of UV radiation associated dermal damage includes, decreased collagen I and III synthesis, increased collagen degradation by TGF-β and activator protein A, infiltration of inflammatory cells predominantly by neutrophils into the dermis releasing ROS (Saha, 2012; Sorg et al., 2005; Talwar et al., 1995). Biomolecules weakly absorb UVA, but it can generate ROS, which oxidize proteins, DNA, and lipids (Cooke et al., 2000; Hattori et al., 1996; Struthers et al., 1998). Cells have developed defense systems to protect themselves from ROS, including endogenous, exogenous and enzymatic antioxidants (Dekker et al., 2005). Heme oxygenase-1 (HO-1) has a cytoprotective function and is strongly inducible in several mammalian cell types by chemical and physical stresses (Elbirt et al., 1999; Noel et al., 1997). This has been shown that HO-1 is highly inducible in skin fibroblasts by UVA; however it does not induce HO-1 expression in human but can induce HO-1 expression in epidermis of hairless mice (Allanson et al., 2004; Applegate et al., 1995; Dekker et al., 2005).

UVB irradiation is a carcinogen and can induce squamous cell carcinomas (Pinnell et al., 2003). As DNA absorbs UVB radiation, DNA mutations can arise. The UV action spectrum for generation of squamous cell carcinoma occurs mostly in the UVB region, though there is some activity in the UVA (Pinnell et al., 2003). While UVB contributes to tumor initiation, UVA primarily causes tumor promotion and generates more oxidative stress due to higher lipid peroxidation efficiency. Additionally, UVA extensively damages DNA by causing strand breaks and oxidation of nucleic acids (Pinnell et al.,

2003). In addition, UVA can induce MMP synthesis that can enhance the aggressiveness of skin cancer. Sunlight can suppress the immune function of skin and promote skin cancer formation (Pinnell et al., 2003). Approximately 40% of human beings are susceptible to UV immunosuppression. Although most studies of UV immunosuppression have been conducted using UVB, recent studies demonstrated the role of UVA in immunosuppression, and the capacity of antioxidants to prevent such immunosuppression (Duthie et al., 1999; Nghiem et al., 2001; Pinnell et al., 2003). Moreover, in addition to more efficiently generating ROS in skin, UVA causes additional biological effects different from UVB. Sunlight contains significantly higher amounts of UVA in comparison to UVB, and the UVB is almost entirely absorbed in the epidermis, while UVA is capable of reaching deeper dermal layers and even disrupting circulating blood cells (Pinnell et al., 2003).

5. The Skin Care Industry

Skin care is the largest of the cosmetic products worldwide, valued at approximately 96 billion in 2011 (Tyrimou, 2012), with the Asia-Pacific accounting for 43% of the skin care market in 2011. (Tyrimou, 2012). What's more, the sales for anti-aging products in North America rose by nearly 14% in 2011 and are estimated to continue to increase around the world (Tyrimou, 2012). The realm of cosmeceuticals is rapidly expanding in numerous countries. This expansion is a result of the availability of new ingredients, the financial rewards for developing successful products, consumer demand, and a better understanding of skin physiology (Tyrimou, 2012). The cosmeceutical industry combines the many skills of cosmetic creators, along with the creativity of marketing experts, the requests of an aging population and the understanding of dermatologists into several products (Giacomoni et al., 1996a).

The search for effective and safe sun protection has propelled cooperation and mutual exchange between scientists within the industry and academia, collaboration most successful within the science field of photobiology (Giacomoni, 2005). Sunscreens are the "gold standard" for photodamage protection (Choudhary et al., 2010). However, it has been shown that sunscreens provide much less protection than expected, but providing a false sense of security. Sun protection factor (SPF) of individual products is measured by testing the efficacy of the component to filter UV at an application rate of 2 mg/cm² of skin (Pinnell et al., 2003). In fact, controlled studies of actual sunscreen usage demonstrated that sunscreens are applied to skin at only 0.5 mg/cm² or less, and given that SPF concentration is not linearly proportional, 0.5 mg/cm² application of high SPF sunscreen to skin only provides less than SPF 3 protection (Autier et al., 2001; Pinnell et al., 2003) (not clear). Moreover, synthetic sunscreens can potentially cause harm as free radicals may be produced by ingredients in the products themselves when activated by UV radiation (Cross et al., 2001; Pinnell et al., 2003). Therefore, such problems enhance the introduction of natural products for sun protection, and are considered safer. As a result, this allows for innovation in the cosmeceutical market to develop safer, naturally derived products. Some of these naturally derived products have proven to be helpful, whereas more evidence is needed for others (Amer et al., 2009).

6. Natural Skin Care Therapy

Due to extensive research on different plant species and associated therapeutic principles, traditional medicine is being re-examined (Moulisha et al., 2010). It has been demonstrated that plants synthesize chemicals with powerful antioxidant activity to control the oxidative stress caused by sunlight and oxygen (Moulisha et al., 2010). Anti-collagenase and anti-elastase activities have been found in secondary metabolites and plant extracts (Thring et al., 2009). Collagenase and elastase are enzymes that contribute to the degradation of collagen within the skin. Several Plant polyphenols such as flavonoids, phenolic acids and tannins have been found to be collagenase inhibitory compounds which may serve as a platform for synthesis of other inhibitory molecules (Kim et al., 2004). Polyphenols, such as epigallocatechin gallate (EGCG), extracted from green tea (*Camellia*

sinensis) have been extensively explored and found to be effective inhibitors with particular good anti-elastase activity at concentrations of 250 µM (Kim et al., 2004; Thring et al., 2009).

Triterpenoids known as boswellic acids isolated from frankincense (*Boswellia spp*.) resin have also indicated anti-elastase activity (Mereish et al., 1991). In a study analysing 150 plants extracts for their ability to inhibit elastase, six showed activity over 65%. These included cinnamon (*Cinnamonum cassia*), turmeric *(Curcuma longa*) and nutmeg (*Myristica fragrans*). Polyphenols isolated from persimmon (*Diospyros kaki*) leaf showed anti-collagenase and anti-elastase activity (Lee et al., 1999; Thring et al., 2009). This activity was thought to be a result of flavonoids present in the polyphenol extract. Plant extracts and natural products which have shown anti-enzyme activity represent a wide variety of the types of phenolic compounds found in plants (Lee et al., 1999; Thring et al., 2009). White tea and cleavers extracts also demonstrated high anti-elastase activity, suppressing over 89% and 57.9% of enzyme activity respectively. Similar anti-elastase effects were observed in burdock root (50.9%), bladderwrack (50.2%), anise (31.9%) and angelica (31.6%) (Thring et al., 2009).

Sunscreens are useful but not ideal due to incomplete spectral protection and risk of toxicity (Pinnell et al., 2003). Antioxidants, common ingredients in cosmeceuticals, have been used by the industry for many years as a result of several benefits such as anti-aging and anti-inflammatory properties. In addition to blocking UV-induced inflammatory pathways, antioxidants provide protection by quenching free radicals (Reszko et al., 2009). While skin uses antioxidants for protection against sun damage (Pinnell et al., 2003), the system can be overwhelmed by excess exposure to various sources of pro-oxidants, which induce oxidative stress (Rabe et al., 2006). UV radiation absorbed by various chromophores in skin result in photochemical reactions (Amer et al., 2009). These reactions result in DNA alterations such as oxidation of nucleic acids and gene mutations and can change proteins and lipids, causing changes in cell function and leading to tissue aging (Amer et al., 2009).

Two mechanisms are involved in free radical natural skin defense: 1) enzymatic defense by glutathione peroxidise and extracellular superoxide dismutase; and 2) non-enzymatic processes through components such as vitamin C, tocopherols and other food derived antioxidants (Pinnell et al., 2003). Antioxidants pair up with free radicals, ultimately minimizing cross linkage and DNA damage (Amer et al., 2009). Topical antioxidants provide a great treatment option due to the close proximity of the molecules to the skin where it can block the solar radiation and as oral antioxidants. In some cases the orally administered components may not reach the skin in sufficient amounts to be effective (Amer et al., 2009; Zhang et al., 1999). However, several recent studies have shown that orally administered components (omega -3-fatty acids, lycopene) are more effective when consumed through diet (beauty from within). Several obstacles exist within the industry regarding effectiveness of topical application of antioxidants: 1) instability, such compounds can be reduced or oxidized easily; 2) color, difficulty to produce an acceptable aesthetic product; 3) lack of adequate skin penetration; 4) photo-protection of the antioxidant etc., (Amer et al., 2009). Recent categories of antioxidants include a wide variety of natural plant components such as polyphenols (Amer et al., 2009).

7. Polyphenols

Polyphenols are a large class of chemical compounds synthesized by plants and are rich in fruits, vegetables, tea, cocoa and other plant products, and have been related to health benefits shown by these products. Polyphenols have antioxidant, anti-inflammatory, anti-carcinogenic and other biological properties which may protect from oxidative stress and several diseases (Kanti et al., 2009). Polyphenols are abundant in nature and extremely diverse with over 8,000 different polyphenolic compounds currently identified (Kanti et al., 2009). Although all polyphenols have similar chemical structures, subtle differences exist which allow for subdivision into main subclasses: phenolic acids, stilbenes, tannins, diferuloylmethanes and flavonoids (Kondratyuk et al., 2004; Kanti et al., 2009; Spencer et al., 2008). Flavonoids and phenolic acids are capable of scavenging free radicals and

chelating metal ions such as iron and copper known to participate in the initiation of free radical reactions (Utara et al., 2009). Flavonoids act as scavengers of free radicals and terminate the process of ROS production as well as inhibit the activities of several redox enzymes, and act in redox-sensitive signalling cascades to inhibit cell damage caused by free radicals (Cao et al., 1996; Parmar et al., 2010; Patel et al., 2005; Robak et al., 1988; Svobodova et al., 2003; Torel et al., 1986).

8. Botanicals for Skin Health

8.1. Soybeans

Soybeans and related food products are a rich source of a subclass of flavonoids called isoflavones (Pinnell et al., 2003). Isoflavones have gained increased popularity because epidemiologic studies suggest that they may be responsible for the lower risk of cardiovascular disease and breast cancer in populations that consume large amounts of soy (Glazier et al., 2001).

The most abundant isoflavones in soy are genistein and daidzein, which are present as glycosides that are converted to the free isoflavones forms (Brandenberger et al., 1997). The glycosides are not estrogenically active, and may be used for topical applications (Miksicek, 1995). Isoflavones are weak estrogens; however their affinity to the estrogen receptor is 4-5 folds lower than the hormonal estrogens. Estrogens function by coupling with estrogen receptors in the nucleus, turning linked genes on or off, which leads to proliferative or differentiation responses. Two types of estrogen receptors (ER) have been identified and are both present in the skin: ER alpha (ER-α) and ER beta (ER-β) (Brandenberger et al., 1997). Genistein has a 30-fold higher affinity for ER-β than ER-α; however, greater ER-α agonist activity has been shown (Barkhem et al., 1998; Katiyar et al., 1999). Bioavailability of isoflavones, just as any other polyphenols, is considerably low. Still, the circulating levels of phytoestrogens are capable of inducing a biological effect (Pinnell et al., 2003). Isoflavones may block the estrogen receptor leading to anti-estrogenic effects (Pinnell et al., 2003). Skin properties change dramatically during and after menopause (Affinito et al., 1999; Brincat et al., 1987; Castelo-Branco et al., 1992). The thickness of the skin reduces along with the collagen content. Oral or topical administration of estrogen has shown to increase thickness and collagen content of skin (Brincat et al., 1987; Castelo-Branco et al., 1992; Maheux et al., 1994; Varila et al., 1995). Genistein might also exhibit collagen-stimulating effects. Throughout studies using skin fibroblasts, genistein increased collagen, type I, alpha 2 (COL1A2) gene expressions (Greenwel et al., 1995) which may be an alternative process independent of the estrogen receptor action (Greenwel et al., 1995).

Genistein is an effective antioxidant, as it scavanges peroxyl radicals and protects against lipid peroxidation in vitro and in vivo (Hwang et al., 2000; Wiseman et al., 2000). This isoflavone has also been shown to inhibit in vitro UV-induced DNA oxidation and reduced hydrogen peroxide–generated DNA damage in human lymphocytes (Giles et al., 1997; Widyarini et al., 2001). This antioxidant has also demonstrated anti-inflammatory properties by suppressing UVB-induced expression of cyclooxygenase-2 in keratinocytes and inhibiting UVB-stimulated prostaglandin E2 synthesis in human epidermal cell cultures (Isoherranen et al., 1999; Miller et al., 1994). Finally, genistein has immune-modulating effects as it has proven to inhibit UV-induced immunosuppression in mice (Widyarini et al., 2001).

8.2. Tea

Tea (*Camellia sinensis*) is a potent source of polyphenols, containing approximately 30% to 35% of the dry weight of the leaf. Tea polyphenols are widely studied for their anticarcinogenic activity mostly in animal models of various cancers including that of skin. Tea polyphenols have shown strong skin cancer inhibition in mouse 2-stage carcinogenesis models (Alexis et al., 1999; Bickers et al., 2000; Bode et al., 2000; Katiyar et al., 1996; Yang et al., 2002). Both oral and topical green tea polyphenols

lowered chemically induced and UV-induced skin tumors (Huang et al., 1992; Wang et al., 1991). Green tea also inhibited growth of established skin tumors, as it prevented conversion of benign skin tumors to squamous cell carcinoma (Miller et al., 1994; Wang et al., 1992). Green tea and black tea were equivalent in effect and decaffeinated tea was shown to be less effective (Wang et al., 1994).

While the nature of anticarcinogenic effect is unknown, tea polyphenols are powerful antioxidants as they quench singlet oxygen, superoxide radical, hydroxyl radical, hydrogen peroxide, and peroxyl radical (Grinberg et al., 1997; Guo et al., 2003; Jovanovic et al., 2000; Reszko et al., 2009; Shi et al., 2000; Unno et al., 2002). It has been shown that tea polyphenols reduced UV-induced lipid peroxidation in skin (Kim et al., 2001) and oxidation of proteins in a free radical–generating system in vitro (Nakagawa et al., 2002). Tea polyphenols also regulate cellular redox signal transduction. In human keratinocytes, (-) epigallocatechin- 3-gallate inhibited factors involved in the photoaging process such as UVB-induced AP-1 activity and mitogen-activated protein kinase cell signaling pathways (Barthelman et al., 1998; Katiyar et al., 2001).

Studies indicate that tea polyphenols are anti-mutagenic. Tea polyphenols protected DNA from oxidation by hydrogen peroxide and UVB in vitro (Wei et al., 1999). In human skin fibroblasts, tea polyphenols protected against radiation-induced DNA damage (Parshad et al., 1998). In Jurkat lymphocytes, epigallocatechin gallate decreased DNA damage caused by free-radical generators and hydrogen peroxide (Johnson et al., 2000). Topical application of green tea polyphenols reduced UVB-induced pyrimidine dimers in epidermis and dermis (Katiyar et al., 2000).

Tea polyphenols have anti-inflammatory effects. Topically applied green tea polyphenols reduced UV-induced erythema and sunburn in human skin (Elmets et al., 2001). Topical (-) epigallocatechin-3-gallate decreased UVB-induced inflammatory responses and infiltration of leukocytes in human skin (Katiyar et al., 1999). Green tea polyphenols also have immune-modulating effects. Green tea polyphenols protected human skin from UV-induced Langerhans cell depletion skin (Elmets et al., 2001). Topical epigallocatechin-3-gallate protected against UVB-induced immunosuppression and tolerance in mice, while topical application of EGCG inhibited carcinogenesis and selectively increased apoptosis in UVB-induced skin tumors in mice (Katiyar et al., 1999; Lu et al., 2002).

In a human study, topical green tea extract inhibited UV-induced erythema and reduced DNA damage (Elmets et al., 2001). In another study, the combined use of oral and topical green tea on the clinical and histologic characteristics of photoaging was evaluated in 40 women with moderate photoaged skin (Chiu et al., 2005). The subjects received a green tea 10% cream plus an oral 300 mg green tea supplementation twice daily or a placebo treatment for 8 weeks. Through patient self-assessments, it was revealed that the green tea group had significant improvements in overall appearance (Chiu et al., 2005). Those receiving the green tea regimen also had a significant improvement in elastic tissue (Chiu et al., 2005).

8.3. Coffee Plant

The whole fruit of the coffee plant has been shown to contain a wide range of polyphenol compounds, including proanthrocyanidins, quinic acid, caffeic acid, caffeine and chlorogenic acid (Lupo et al., 2007). In the past, coffee growers discarded the fruit of the coffee plant, harvesting the coffee bean alone, however in vitro and ex vivo studies revealed that the outer fruit of the coffee plant has effective hydroxyl radical scavenging activity (Baumann, 2007a). Another study also found a positive relation between the level of chlorogenic acid in the extract and antioxidant activity (Baumann, 2007a). Additionally it was shown that caffeic acid inhibits UVB induced expression of COX-2 which can eventually lead to skin cancer (Kang et al., 2009). Moreover, positive effects on UVB induced carcinogenesis, as well as patches induced by UVB were ameliorated with caffeine administration and

topical application respectively in mice (Conney et al., 2008). In addition, co-incubation with quinic acid prevented skin death that was caused by UV damage in skin cultures (Mammone et al., 2006).

8.4. Fern

The extract of the *Polypodium leucotomos* (PL), a fern plant grown in Central America, was found to contain active components which include a variety of phenolic compounds such as p-coumaric, ferulic, caffeic, vanillic, and chlorogenic acids (Gombau et al., 2006). These compounds have shown to retain antioxidant, photoprotective, and chemopreventive properties, inhibiting lipid peroxidases and scavanging free radicals (Gombau et al., 2006; Middelkamp-Hup et al., 2004). PL appeared to be an effective photoprotective agent post oral administrations. It has been shown that there was a significant decrease in erythema in treated skin in healthy participants exposed to varying doses of UV radiation; with or without an oral administration of the extract (Middelkamp-Hup et al., 2004). Histologically, treated skin was characterized by less epidermal damage, fewer cells with sunburn, and fewer cyclobutane pyrimidine dimers (mutagenic and carcinogenic compounds), less epidermal proliferation, and less dermal mast cell infiltration (Middelkamp-Hup et al., 2004). Moreover, PL was also able to suppress the production of ROS that was induced by UV, therefore acting as antioxidant agent (Gonzalez et al., 2011). In addition, orally administered PL to mice resulted in inhibition of UVB radiation that triggered skin cancer (Siscovick et al., 2008).

8.5. Pine Bark

Pycnogenol™ is an extract from French maritime pine bark which contains several phenolic and polyphenolic flavonoids (Berson, 2008; Yoshikawa et al., 1990). Antioxidant properties of such compounds include prevention of lipid peroxidation and reductions in oxidative stress via an increase in glutathione (GSH) and the GSH antioxidant defense enzymes (Sime et al., 2004; Yoshikawa et al., 1990). In a mouse model, when a pycnogenol extract was applied after daily irradiation, UV radiation-induced inflammation, immunosuppression and carcinogenesis were reduced (Kanti et al., 2009; Yoshikawa et al., 1990). The wound-healing properties of this extract were further confirmed in an experimental rat model, where application of a Pycnogenol™ 1% to 5% gel significantly shortened wound healing time in a dose-dependent manner (Brincat et al., 1965). Moreover, Pycnogenol™ supplementation resulted in beneficial effects on skin hydration as well as skin elasticity which are mediated by hyaluronic acid and collagen, therefore suggesting this compound role in skin aging (Marini et al., 2012).

8.6. Mushroom

Various types of mushrooms such as shiitake and reishi have been consumed by people in many Asian countries for centuries (Berson et al., 2008). Mushroom extracts have been shown to have potent antioxidant and anti-inflammatory properties, including inhibition of lipid peroxidation, activities of superoxide dismutase and metalloproteinases, and levels of proinflammatory cytokines (Berson et al., 2008; Mau et al., 2002). In addition to these effects, the shiitake complex has been shown to inhibit the enzymes elastase, involved in elastin breakdown, and AP-1, involved in collagen break down (Berson et al., 2008). Moreover, a study on 45 healthy adults demonstrated that mushroom extracts stimulated growth of epidermal skin cells (Berson et al., 2008). Mushroom complex was applied as a serum twice daily or as a cream once daily to randomized sites of treatment (Nebus et al., 2007). Sites treated with all formulations of the mushroom extract were associated with significantly faster cell turnover rates compared with untreated sites of control subjects (Nebus et al., 2007). Similar effects were observed in a study involving 31 women subjects with moderate facial photodamage. Assessments revealed significant improvements in skin texture, clarity, a reduction in overall photoaging, fine lines, and pigmentation within only 8 weeks of treatment (Nebus et al., 2007).

8.7. Milk Thistle

Silymarin, a flavonoid isolated from milk thistle plant, is composed of different flavonolignans including silybin, silidianin, silychristin and isosylibin (Mereish et al., 1991; Wagner et al., 1974). Silybin shows more antioxidant and anti-inflammatory properties than other compounds in milk thistle, and is known to be an antioxidant compound with skin cancer chemopreventive properties (Comoglio et al., 1990; Wagner et al., 1974). Several experiments show that topical application of silymarin significantly inhibited UVB-induced skin edema, formation of sunburn and apoptotic cells (Katiyar et al., 1997). This evidence suggested that silymarin might provide protection against different stages of UVB-induced carcinogenesis (Afaq et al., 2002). It was shown that topical application of silymarin protects against UVB radiation-induced non-melanoma skin cancer in mice (Afaq et al., 2002). Female SKH-1 hairless mice were subjected to UVB-induced tumor initiation, phorbol ester-mediated tumor promotion; as well as DMBA-induced tumor initiation, UVB-mediated tumor promotion, and UVB-induced complete carcinogenesis (Katiyar et al., 1997). In all three procedures, topical application of silymarin prior to UVB irradiation/DMBA exposure significantly lowered tumor incidence, tumor multiplicity per mouse, and average tumor volume (Afaq et al., 2002).

8.8. Grape Seed

Grape seed extracted from various plants such as grapes are rich in pro-anthocyanidins, part of the flavonoid family (Vinson et al., 1995). Pro-anthocyanidins are powerful antioxidants with strong free radical scavenging activities (Guo et al., 1996). A potential antioxidant mechanism of photo protection by grape seed proanthocyanidins (GSP) has been suggested, as GSP inhibited the depletion of antioxidant defense components caused by UVB and appears to enhance SPF in humans (Afaq et al. 2003; Mantena et al., 2006; Mittal et al., 2003). Additionally, grape seed extract demonstrated photochemopreventive effects on skin cancer induced by UVB (Perde-Schrepler et al., 2012). Moreover, oral administration of this compound was also beneficial in reducing hyperpigmentaion (Baumann, 2007b). Additionally, grape seed extract supplemented mice noticed chemopreventive effects on skin cancer induced by UV (Filip et al., 2011a; 2011b). Furthermore, oxidative stress and apoptosis induced by UVB in skin was reduced when mice consumed grape seed extract (Filip et al., 2013).

8.9. Sea Buckthorn (SBT)

SBT is thorny nitrogen fixing deciduous shrub native to Europe and Asia, which is used as a medicinal plant in Tibetan and Mongolian traditional medicines (Lu, 1992; Patel et al., 2012; Rousi et al., 1971). Since the 1950's, many curative preparations of SBT have been clinically used to treat radiation damage, burns, oral inflammation and gastric ulcers in China and the former Soviet Republics (Fu et al., 1993; Geetha et al., 2002; Isoherranen et al., 1999; Mereish et al., 1991).

Leaf and fruit extracts of SBT at a concentration of 500 µg/ml were found to inhibit chromium-induced free radical production, apoptosis, and DNA fragmentation, and restored the antioxidant status. This data suggests that these extracts have cytoprotective properties, which may contribute to the anti-oxidant activity (Geetha et al., 2002). More than 200 bioactive components have been found in SBT plant, containing several chemical compounds including carotenoids, tocopherols, sterols, flavonoids, phenolics, lipids, and ascorbic acid. These compounds are of interest due to their biological and therapeutic activities including antioxidant and antiproliferative effects, hepatoprotective effects, antimicrobial effects and immunomodulation effects (Cheng et al., 2003; Christaki et al., 2012; Geetha et al., 2008; Grey et al., 2010; Nemtanu et al., 2009).

Berries of the SBT are an excellent source of phytochemicals such as ascorbic acid, tocopherols, unsaturated FA, phenols, and carotenoids. Berries have been used for the treatment of radiation

damage, burns, oral inflammation, and gastric ulcers (Kumar et al., 2011). Other observed positive health effects include reduction in plasma cholesterol level, inhibition of platelet aggregation, and regulation of immune function (Yang et al., 2002). Study findings reported that phenolics were main contributors to the antioxidant activity of SBT berries, leading to increased focus on using SBT berries for medical and cosmetic purposes as well as functional foods (Beveridge et al., 1999; Greenwel et al., 1995; Yoshikawa et al., 1990; Zhang et al., 1989). Seventeen phenolic acids were tentatively identified in SBT berries. Salicylic acid was the predominant phenolic acid, as it constituted between 55.0% (Otradnaja and Trofimowskaja cultivars) and 74.3% (Nevlejena cultivar) of the total phenolic acids present (Zadernowski et al., 2005). Another study tentatively identified only four phenolic acids, namely p-coumaric, ferulic, p-hydroxybenzoic, and ellagic acids in SBT berries harvested in Finland (Hakkinen et al., 2000).

Phytosterols are main constituents of sea buckthorn oils. β-sitosterol and 5-avenasterol are the major phytosterols found in sea buckthorn oil (Bal et al., 2011). The amount of phytosterol in SBT is significantly high and may exceed soybean oil by 4–20 times. Research indicates that the total phytosterol content, varied between subspecies and collection sites, in the seeds, fresh pulp/peel, and the whole berries were 1200–1800, 240–400, and 340–520 mg/kg, respectively (Yang et al., 2001).

9. Conclusion

Oxidative stress can occur from many internal and external factors including metabolism, pollution, and sunlight radiation. A wide variety of information supports the photocarcinogenic damage to the skin from sunlight and its relationship to oxidative stress. Antioxidants work together in skin, supporting and regenerating each other. Topical antioxidants may provide several advantages for photoprotection not provided by dietary supplements alone. As antioxidants are delivered into skin, they can provide protection by accumulating in pharmacologic concentrations and targeting exposed skin. As oxidative stress depletes natural antioxidant stores, these concentrations offer protection by supplementing reserves.

There are several natural ingredients found in many plants with antioxidant and anti-inflammatory properties that appear to be effective for photoprotection (see Figure 2). More notably, some of these agents such as soy, mushroom extracts, and tea, also have chemopreventive properties that offer potential for the prevention/treatment of skin diseases and cancers. The botanical compounds discussed here show significant anti-inflammatory, antioxidant and cell protective effects. These protective effects may contribute to their anti-photocarcinogenic effects and act to inhibit various biochemical processes induced by solar UV radiation. Based on the epidemiological evidence and laboratory studies conducted using in vitro and in vivo systems, it is suggested that regular consumption and topical treatment of these polyphenols may provide effective protection against the harmful effects of aging and UV radiation.

Consumer-driven demand has led to rapid development of products to counteract signs of aging skin. Botanicals found in cosmeceuticals may offer skin protection from photodamage and repair skin by improving or stimulation of new collagen production.

Combined with sunscreens and other sun protection, cosmeceuticals can help enhance skin appearance and health. More importantly, as many cosmeceuticals claim different effects, future trends should include multifunctional cosmetics which will allow for optimal skin health benefits to be plausible.

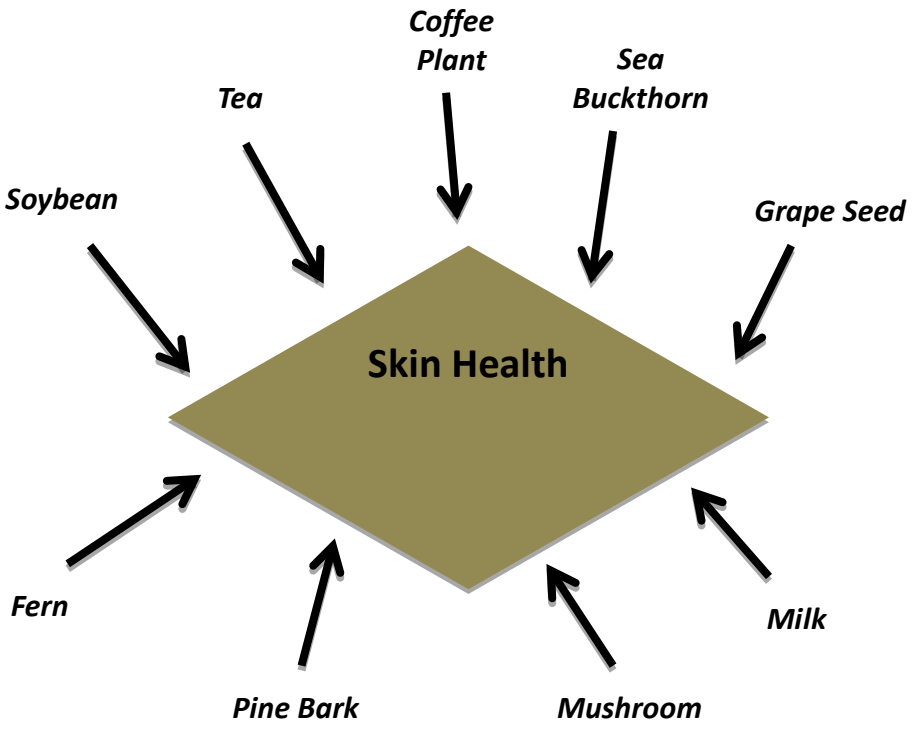

Figure 2: *Botanicals Beneficial for Skin Health*

References

Afaq, F., Adhami, V.M., Ahmad, N., and Mukhtar, H. *Botanical Antioxidants for Chemoprevention of Photocarcinogenesis*. Frontiers in Bioscience. 2002. 7; 784-792.

Afaq, F., Adhami, V.M., and Ahmad, N. *Prevention of Short-Term Ultraviolet B Radiation-Mediated Damages by Resveratrol in SKH-1 Hairless Mice.* Toxicol Appl Pharmacol. 2003. 186 (1) 28-37.

Affinito, P., Palomba, S., Sorrentino, C., Di Carlo, C., Bifulco, G., Arienzo, M.P., and Nappi, C. *Effects of Postmenopausal Hypoestrogenism on Skin Collagen*. Maturitas. 1999. 33 (3) 239-247.

Allanson, M., and V.E., Reeve. *Immunoprotective UVA (320400 nm) Irradiation Upregulates Heme Oxygenase-1 in the Dermis and Epidermis of Hairless Mouse Skin*. J Investig Dermatol. 2004. 122 (4) 1030-1036.

Alexis, A.F., Jones, V.A., and Stiller, M.J. *Potential Therapeutic Applications of Tea in Dermatology.* Int J Dermatol. 1999. 38; 735-743.

Amer, Mohamed and Mina Maged. *Cosmeceuticals versus Pharmaceuticals.* Clinics in Dermatology. 2009. 27 (5) 428-430.

Ameyar, M., Wisniewska, M., and Weitzman, J.B. *A Role for AP-1 in Apoptosis: the Case for and Against. Biochimie.* 2003. 85 (8) 747-752.

Applegate, L.A., and E., Frenk. *Oxidative Defense in Cultured Human Skin Fibroblasts and Keratinocytes from Sun-Exposed and Nonexposed Skin.* Pholodermalol Photoimmunol Photomed. 1995. 11 (3) 95-101.

Autier, P., Boniol, M., Severi, G., and Doré, J.F. *The European Organization for Research and Treatment of Cancer Melanoma Co-Operative Group. Quantity of Sunscreen used by European Students.* British Journal of Dermatology. 2001. 144; 288-291.

Bal, L.M., Meda, V., Naik, S.N., and Satya, S. *Sea Buckthorn Berries: A Potential Source of Valuable Nutrients for Nutraceuticals and Cosmoceuticals.* Food Research International. 2011. 44 (7) 1718-1727.

Barkhem, T., et al. *Differential Response of Estrogen Receptor Alpha and Estrogen Receptor Beta to Partial Estrogen Agonists/Antagonists.* Mol Pharmacol. 1998. 54 (1) 105-112.

Barthelman, M., et al. (—)-*epigallocatechin-3-gallate Inhibition of Ultraviolet B Induced AP-1 Activity.* Carcinogenesis. 1998. 19 (12) 2201-2204.

Baumann, L.S., 2007a: Coffea Arabica and CoffeeBerry Extract. Skin and Allergy News. Retreived from www.skinandallergynews.com.

Baumann, LS. *Less-known Botanical Cosmeceuticals.* Dermatologic Therapy. 2007b. 20 (5) 330-342.

Beveridge, T., T.S.C., Li, B.D., Oomah and A., Smith. *Sea Buckthorn Products: Manufacture and Composition.* J Agric Food Chem. 1999. 47 (9) 3480-3488.

Benaiges, A., Marcet, P., Armengol, R., Betes, C., Girones, E. *Study of the Refirming Effect of a Plant Complex.* Int J Cosmet Sci. 1998. 20 (4) 223-233.

Berson, D.S. *Natural Antioxidants.* Journal of Drugs in Dermatology. 2008. 7 (7) s7-12. Retrieved from http://search.proquest.com/docview/69398074?accountid=11233

Bickers, D.R., and Athar, M. *Novel Approaches to Chemoprevention of Skin Cancer.* J Dermatol. 2000. 27 (11) 691-695.

Biswa, M., Bhattacharya, S., Ghosh, A.K., and Haldar, P.K. *Evaluation of Vitro Antioxidant and Free Radical Scavenging Effects Of Terminalia Arjuna Leaf.* Pharmacologyonline. 2010. 3; 392-400.

Bode, A.M., and Dong, Z. *Signal Transduction Pathways: Targets for Chemoprevention of Skin Cancer*. Lancet Oncology. 2000. 1; 181-188.

Brandenberger, A.W., et al. *Tissue Distribution of Estrogen Receptors Alpha (er-alpha) and Beta (er-beta) mRNA in the Midgestational Human Fetus.* J Clin Endocrinol Metab. 1997. 82 (10) 3509-3512.

Brincat, M., et al. *Long-term Effects of the Menopause and Sex Hormones on Skin Thickness.* Br J Obstet Gynaecol. 1985. 92 (3) 256-259.

Brincat, M., et al. *Skin Collagen Changes in Post-Menopausal Women Receiving Oestradiol Gel*. Maturitas. 1987. 9 (1) 1-5

Brooker, Robert J., 2011: *Genetics: Analysis and Principles.* 4th Ed. McGraw-Hill Science.

Castelo-Branco, C., et al. *Skin Collagen Changes Related to Age and Hormone Replacement Therapy.* Maturitas. 1992. 15 (2) 113-119.

Cao, G., Sofic, E., and Prior, R.L. *Antioxidant and Prooxidant Behavior of Flavonoids: Structure-Activity Relationships.* Free Radic Biol Med. 1996. 22 (5) 749-760.

Cheng, J., Kondo, K., Suzuki, Y., Ikeda, Y., Meng, X., and Umemura, K. *Inhibitory Effects of Total Flavones of Hippophae Rhamnoides L. on Thrombosis in Mouse Femoral Artery and in vitro Platelet Aggregation.* Life Science. 2003. 72 (20) 2263-2271.

Chiu, A.E., Chan, J.L., Kern, D.G., et al. *Double-blinded, Placebo-Controlled Trial of Green Tea Extracts in the Clinical and Histological Appearance of Photoaging Skin*. Dermatol Surg. 2005. 31 (7 Pt.2) 855-859.

Choudhary, S., et al. *Photodamage, Part 1: Pathophysiology, Clinical Manifestations, and Photoprotection.* Cosmetic Dermatology. 2010. 23 (10) 460-467.

Chung, J.H., Kang, S., Varani, J., Lin, J., Fisher, G.J. and Voorhees, J.J. *Decreased Extracellular-Signal-Regulated Kinase and Increased Stress-Activated MAP Kinase Activities in Aged Human Skin in vivo.* Journal of Investigative Dermatology. 2000. 115 (2) 177-182.

Conney, A.H., Kramata, P., Lou, Y.R., & Lu, Y.P. *Effect of Caffeine on UVB-induced Carcinogenesis, Apoptosis, and the Elimination of UVB-induced Patches of p53 Mutant Epidermal Cells in SKH-1 Mice.* Photochemistry and Photobiology. 2008. 84 (2) 330-338.

Christaki E. *Hippophae Rhamnoides L. (Sea Buckthorn): a Potential Source of Nutraceuticals.* Food and Public Health. 2012. 2 (3) 69-72.

Comoglio, A., G., Leonarduzzi, R., Carini, D., Busolin, H., Basaga, E., Albano, A., Tomasi, G., Polio, P., Morazzoni and M.J., Magistretti. *Studies on the Antioxidant and Free Radical Scavenging Properties of IdB 1016: a New Flavanolignan Complex*. Free Radic Res Commun. 1990. 11 (1-3) 109-115.

Crisan, M., Badea, R., Cattani, C., and Crisan, D., 2012: *Senescence: Imagistic Noninvasive Assessment of Skin Aging and Anti-Aging Therapies, Senescence*, Dr. Tetsuji Nagata (Ed.). Intech

Cooper, K.D., Oberhelman, L., Hamilton, T.A., Baadsgaard, O., Terhune, M., Levee, G., Anderson, T. and Koren, H. *UV Exposure Reduces Immunization Rates and Promotes Tolerance to Epicutaneous Antigens in Humans: Relationship to Dose, CD la-DR1 Epidermal Macrophage Induction, and Langerhans Cell Depletion.* Proc. Natl. Acad. Sci. 1992. 89; 8497-8501.

Cooper, K.D. *Effects of UV Radiation from Artificial Light Sources on the Human Immune System.* Photochem Photobiol. 1995. 61; 231-235.

Cooke, M.S., N., Mistry, A., Ladapo, K.E., Herbert and J., Lunec. *Immunochemical Quantitation of UV-Induced Oxidative and Dimeric DNA Damage to Human Keratinocytes.* Free Radical Res. 2000. 33 (4) 369-381.

Cross, S.E., Jiang, R.Y., Benson, H.A.E., Roberts, M.S. *Can Increasing the Viscosity of Formulations Be Used to Reduce the Human Skin Penetration of the Sunscreen Oxybenzone?* J Invest Dermatol. 2001. 117 (1) 147-150.

Damian, D.L., Halliday, G.M., and Barnetson, R.C. *Broad Spectrum Sunscreen Provides Greater Protection Against Ultraviolet-Radiation Induced Suppression of Contact Hypersensitivity to a Recall Antigen in Humans.* J Invest Dermatol. 1997. 109; 146-151.

Dekker, Pim, Parish, William, E., Green, Martin, R. *Protection by Food-derived Antioxidants from UV-A1–Induced Photodamage, Measured Using Living Skin Equivalents.* Photochemistry and Photobiology. 2005. 81 (4) 837-842.

Duthie, M.S., Kimber, I., and Norval, M. *The effects of Ultraviolet Radiation on the Human Immune System.* Br J Dermatol. 1999. 140 (6) 995-1009.

Elbirt, K.K., and H.L., Bonkovsky. *Heme Oxygenase: Recent Advances in Understanding Its Regulation and Role*. Proc Asso Am Physicians. 1999. 111 (5) 438-447.

Elmets, C.A. et al. *Cutaneous Photoprotection from Ultraviolet Injury by Green Tea Polyphenols*. J Am Acad Dermatol. 2000. 44 (3) 425-432.

Fisher, G.J., Kang, S., Varani, J., Bata- Csorgo, Z., Wan, Y., Datta, S., et al. *Mechanisms of Photoaging and Chronological Skin Aging.* Archives of Dermatology. 2002. 138 (11) 1462-1470.

Filip, A., Daicoviciu, D., Clichici, S., Mocan, T., Muresan, A., and Postescu, I.D. *Photoprotective Effects of Two Natural Products on Ultraviolet B–Induced Oxidative Stress and Apoptosis in SKH-1 Mouse Skin.* Journal of Medicinal Food. 2011a. 14 (7-8) 761-766.

Filip, A., Daicoviciu, D., Clichici, S., Bolfa, P., Catoi, C., Baldea, I. and Postescu, I.D. *The effects of grape seeds polyphenols on SKH-1 mice skin irradiated with multiple doses of UV-B.* Journal of Photochemistry and Photobiology B: Biology. 2011b. 105 (2) 133-142.

Filip, G.A., Postescu, I.D., Bolfa, P., Catoi, C., Muresan, A. and Clichici, S. *Inhibition of UVB-induced Skin Phototoxicity By A Grape Seed Extract As Modulator of Nitrosative Stress, ERK/NF-kB Signaling Pathway and Apoptosis, in SKH-1 mice.* Food and Chemical Toxicology. 2013. 57; 296-306.

Fu, Q., Yang, Q., and Yang, G. *Analysis of Alpha-Tocopherol Contents in Seabuckthorn Oil by Reversed Phase-High Performance Liquid Chromatography.* Journal of Xi'an Medical University. 1993. 14; 181-183.

Geetha, S., et al. *Anti-Oxidant and Immunomodulatory Properties of Seabuckthorn (Hippophae Rhamnoides) - an in Vitro Study*. J Ethnopharmacology. 2002. 79 (3) 373-378.

Geetha, S., Jayamurthy, P., Pal, K., Pandey, S., Kumar, R., and Sawhney, R.C. *Hepatoprotective Effects of Sea Buckthorn (Hippophae rhamnoides L.) Against Carbon Tetrachloride Induced Liver Injury in Rats.* Journal of the Science of Food and Agriculture. 2008. 88 (9) 1592-1597.

Giacomoni, P., 2005: Aging, Science and the Cosmetics Industry. The Micro-Inflammatory Model Serves as a Basis for Developing Effective Anti-Aging Products for the Skin. EMBO Reports 6 Spec: S45-48.

Giacomoni, P.U., and D'Alessio, P., 1996a: *Skin Aging: the Relevance of Anti-Oxidants*. In: Rattan SIS, Toussaint O (Eds). Molecular Gerontology. NY, USA: Plenum.

Giacomoni, P.U., and D'Alessio, P. *Open Questions in Photobiology. IV. Photoaging of the Skin.* J Photochem Photobiol B. 1996b. 33 (3) 267-272.

Giacomoni, P.U., and Rein, G. *Factors of Skin Aging Share Common Mechanisms.* Biogerontology. 2001. 2 (4) 219-229.

Giacomoni, P.U. *Aging and Cellular Defence Mechanisms*. Ann NY Acad Sci. 1992. 663: 1-3.

Gilchrest, B.A. *Skin Aging and Photoaging: An Overview*. J Am Acad Dermatol. 1989. 21 (3 Pt 2) 610-613.

Giles, D., et al. *Effect of Structurally Related Flavones/Isoflavones on Hydrogen Peroxide Production and Oxidative DNA Damage in Phorbol Ester-Stimulated Hl-60 Cells.* Nutr Cancer. 1997. 29 (1) 77-82.

Glazier, M.G., et al. *A Review of the Evidence for the Use of Phytoestrogens as a Replacement for Traditional Estrogen Replacement Therapy.* Arch Intern Med. 2001. 161 (9) 1161-1172.

Gonzalez, S., Gilaberte, Y., Philips, N., and Juarranz, A. *Fernblock, a Nutriceutical with Photoprotective Properties and Potential Preventive Agent for Skin Photoaging and Photoinduced Skin Cancers.* Int J Mol Sci. 2011. 12 (12) 8466-8475.

Greenwel, P., et al*. Tyrosine Dephosphorylation of Nuclear Proteins Mimics Transforming Growth Factor beta-1 Stimulation of Alpha-2 (I) Collagen Gene Expression.* Mol Cell Biol. 1995. 15 (12) 6813-6819.

Grey, C., Widén, C., Adlercreutz, P., Rumpunen, K., and Duan, R. *Antiproliferative Effects of Sea Buckthorn (Hippophae rhamnoides L.) Extracts on Human Colon and Liver Cancer Cell Lines.* Food Chemistry. 2010. 120 (4) 1004-1010.

Grinberg, L.N., et al. *Protective Effects of Tea Polyphenols against Oxidative Damage to Red Blood Cells.* Biochem Pharmacol. 1997. 54 (9) 973-978.

Gombau, L., Garcia, F., Lahoz, A., et al. *Polypodium Leucotomos Extract: Antioxidant Activity and Disposition.* Toxicol in Vitro. 2006. 20 (4) 464-471.

Guo, C., Yang, J., Wei, J., Li, Y., Xu, J., and Jiang, Y. *Antioxidant Activities of Peel, Pulp and Seed Fractions of Common Fruits as Determined by FRAP Assay*. Nutrition Research. 2003. 23 (12) 1719-1726.

Guo, Q., et al. *Studies on Protective Mechanisms of Four Components of Green Tea Polyphenols against Lipid Peroxidation in Synaptosomes*. Biochim Biophys Acta. 1996. 1304 (3) 210-222.

Häkkinen, S., M., Heinonen, S., Karenlampi, H., Mykkanen, J., Ruuskanen, and R., Torronen. *Screening of Selected Flavonoids and Phenolic Acids in 19 Berries.* Food Res Int. 2000. 32 (5) 345-353.

Han, D., Williams, E., and Cadenas, E. *Mitochondrial Respiratory Chain-Dependent Generation of Superoxide Anion and Its Release into the Intermembrane Space.* Biochem J. 2001. 353 (Pt 2) 411-416.

Hattori, Y., C., Nishigori, T., Tanaka, K., Uchida, O., Nikaido, T., Osawa and H., Hiai, S., Imamura and S., Toyokuni. *8-hydroxy-29-deoxyguanosine is increased In Epidermal Cells of Hairless Mice after Chronic Ultraviolet B Exposure.* J Investig Dermatol. 1996. 107 (5) 733-737.

Helfrich, Y.R., Sachs, D.L., and Voorhees, J.J. *Overview of Skin Aging and Photoaging.* Dermatology Nursing. 2008. 20 (3) 177-83 quiz 184.

Huang, M.T., et al. *Inhibitory Effect of Topical Application of a Green Tea Polyphenol Fraction on Tumor Initiation and Promotion in Mouse Skin.* Carcinogenesis. 1992. 13 (6) 947-954.

Hwang, J., et al. *Synergistic Inhibition of LDL Oxidation by Phytoestrogens and Ascorbic Acid.* Free Radic Biol Med. 2000. 29 (1) 79-89.

Isoherranen, K., et al. *Ultraviolet Irradiation Induces Cyclooxygenase-2 Expression in Keratinocytes.* Br J Dermatol. 1999. 140 (6) 1017-1022.

Johnson, M.K., and G., Loo. *Effects of Epigallocatechin Gallate and Quercetin on Oxidative Damage to Cellular DNA.* Mutation Research. 2000. 459 (3) 211-218.

Jovanovic, S.V., et al. Antioxidants in Nutrition Ann N Y Acad Sci. 2000. 899; 326.

Kang, N.J., Lee, K.W., Shin, B.J., Jung, S.K., Hwang, M.K., Bode, A.M. and Dong, Z. *Caffeic acid, A Phenolic Phytochemical in Coffee, Directly Inhibits Fyn Kinase Activity and UVB-induced COX-2 Expression.* Carcinogenesis. 2009. 30 (2) 321-330.

Katiyar, S.K., Perez, A., and Mukhtar, H. *Green Tea Polyphenol Treatment to Human Skin Prevents Formation of Ultraviolet Light B-induced Pyrimidine Dimers in DNA.* Clin Cancer Research. 2000. 6 (10) 3864-3869.

Katiyar, S.K., et al. *Prevention of UVB-induced Immunosuppression in Mice by the Green Tea Polyphenol (—)-epigallocatechin-3-gallate may be Associated with Alterations in IL-10 and IL-12 Production.* Carcinogenesis. 1999. 20 (11) 2117-2124.

Katiyar, S.K., N.J., Korman, H., Mukhtar and R., Agarwal. *Protective Effects of Silymarin against Photocarcinogenesis in a Mouse Skin Model.* J Natl Cancer Inst. 1997. 89 (8) 556-566.

Katiyar, S.K., et al. *Tea Consumption and Cancer.* World Rev Nutr Diet. 1996. 79; 154-184.

Katiyar, S.K., et al. *Protection against Malignant Conversion of Chemically Induced Benign Skin Papillomas to Squamous Cell Carcinomas in SENCAR Mice by a Polyphenolic Fraction Isolated from Green Tea.* Cancer Res. 1993. 53 (22) 5409-5412.

Katiyar, S.K., et al. *Inhibition of UVB-induced Oxidative Stress-Mediated Phosphorylation of Mitogen-Activated Protein Kinase Signaling Pathways in Cultured Human Epidermal Keratinocytes by Green Tea Polyphenol (—)-epigallocatechin-3-gallate.* Toxicol Appl Pharmacol. 2001. 176 (2) 110-117.

Kaur, G., Jabbar, Z., Athar, M., and Alam, M.S. *Punica granatum (pomegranate) Flower Extract Possesses Potent Anti-Oxidant Activity and Abrogates Fe-NTA Induced Hepatotoxicity in Mice.* Food Chem Toxicol. 2006. 44 (7) 984-993.

Kim, J., et al. *Protective Effects of (—)-epigallocatechin-3-gallate on UVA- and UVB-induced Skin Damage.* Skin Pharmacol Appl Skin Physiol. 2001. 14 (1) 11-19.

Kim, Y., Uyama, H., and Kobayashi, S. *Inhibition Effects of (+)-catechin-aldehyde polycondensates on Proteinases Causing Proteolytic Degradation of Extracellular Matrix.* Biochem Biophys Res Commun. 2004. 320 (1) 256-261.

Kondratyuk, T.P., and Pezzuto, J.M. *Natural Product Polyphenols of Relevance to Human Health.* Pharm Biol. 2004. 42 (s1) 46-63.

Kosmadaki, M.G., and Gilchrest, B.A. *The Role of Telomeres in Skin Aging/Photoaging.* Micron. 2004. 35 (3) 155-1

Kuiper, G.G., et al. *Comparison of the Ligand Binding Specificity and Transcript Tissue Distribution of Estrogen Receptors Alpha and Beta.* Endocrinology. 1997. 138 (3) 863-870.

Kumar, R., Kumar, G., Chaurasia, O., and Singh, S. *Phytochemical and Pharmalogical of Seabuckthorn Oil: A Review.* Res J Med Plants. 2011. 5 (5) 491-499.

Lebedeva, L., Rachmov, I., and Kchai darov, K., 1989: Screening Investigation of the Anti-Inflammation Activity of Seabuckthorn Oil. Proceedings of the International Symposium on Seabuckthorn, Xi'an, China. 398-399S.

Lee, K.K., Kim, J.H., Cho, J.J., Choi, J.D. *Inhibitory Effects of 150 Plant Extracts on Elastase Activity, and Their Anti-Inflammatory Effects.* Int J Cosmet Sci. 1999. 21 (2) 71-82.

Lu, Y-P., et al. *Topical Applications of Caffeine or (—)-epigallocatechin gallate (EGCG) Inhibit Carcinogenesis and Selectively Increase Apoptosis in UVB-induced Skin Tumors in Mice.* Proc Natl Acad Sci USA. 2002. 99 (19) 12455-12460.

R., Lu, 1992: *Seabuckthorn: A Multipurpose Plant Species for Fragile Mountains.* ICIMOD Publication Unit, Katmandu, Nepal.

Lupo, M., et al. *CoffeeBerry: A New, Natural Antioxidant in Professional Antiaging Skin Care.* Cosmetic Dermatology. 2007. 20 (No. 10 s4) 1-9.

Maheux, R., et al. *A Randomized, Double-Blind, Placebo-Controlled Study on the Effect of Conjugated Estrogens on Skin Thickness.* Am J Obstet Gynecol. 1994. 170 (2) 642-649.

Mammone, T., Åkesson, C., Gan, D., Giampapa, V., and Pero, R.W. *A Water Soluble Extract From Uncaria Tomentosa (Cat's Claw) is a Potent Enhancer of DNA Repair in Primary Organ Cultures of Human Skin.* Phytotherapy Research. 2006. 20 (3) 178-183.

Mantena, S.K., and Katiyar, S.K. *Grape Seed Proanthocyanidins Inhibit UV-radiation-induced Oxidative Stress and Activation of MAPK and NF-kappaB Signaling in Human Epidermal Keratinocytes.* Free Radic Biol Med. 2006. 40 (9) 1603-1614.

Marini, A., Grether-Beck, S., Jaenicke, T., Weber, M., Burki, C., Formann, P., and Krutmann, J. *Pycnogenol® Effects on Skin Elasticity and Hydration Coincide with Increased Gene Expressions of Collagen Type I and Hyaluronic Acid Synthase in Women.* Skin Pharmacol Physiol. 2012. 25 (2) 86-92.

Mau, J-L., Lin, H-C., and Chen, C-C. *Antioxidant Properties of Several Medicinal Mushrooms.* J Agric Food Chem. 2002. 50 (21) 6072-6077.

Mereish, K.A., D.L., Bunner, D.R., Ragaland and D.A., Creasia. *Protection against Microcystin-LR-Induced Hepatotoxicity by Silymarin: Biochemistry, Histopathology and Lethality.* Pham Res. 1991. 8 (2) 273-277.

Middelkamp-Hup, M.A., Pathak, M.A., Parrado, C., et al. *Oral Polypodium leucotomos Extract Decreases Ultraviolet-Induced Damage of Human Skin.* J Am Acad Dermatol. 2004. 51 (6) 910-918.

Miksicek, R.J. *Estrogenic Flavonoids - Structural Requirements for Biological Activity.* Proc Soc Exp Biol Med. 1995. 208 (1) 44-50.

Miller, C.C., et al. *Ultraviolet-B Injury Increases Prostaglandin Synthesis through a Tyrosine Kinase-Dependent Pathway - Evidence for UVB-Induced Epidermal Growth Factor Receptor Activation.* J Biol Chem. 1994. 269 (5) 3529-3533.

Mittal, A., Elmets, C.A., and Katiyar, S.K. *Dietary Feeding of Proanthocyanidins from Grape Seeds Prevents Photocarcinogenesis in SKH-1 Hairless Mice: Relationship to Decreased Fat and Lipid Peroxidation.* Carcinogenesis. 2003. 24 (8) 1379-88.

Morison, W.L., Pike, R.A., and Kripke, M.L. *Effect of Sunlight and Its Component Wavebands on Contact Hypersensitivity in Mice and Guinea Pig.* Photodermatol. 1985. 2 (4) 195-204.

Muller, Florian. *The Nature and Mechanism of Superoxide Production by the Electron Transport Chain: Its Relevance to Aging*. AGE. 2000. 23 (4) 227-253.

Nakagawa, T., et al. *Protective Activity of Green Tea against Free Radical- and Glucose-Mediated Protein Damage.* J Agric Food Chem. 2002. 50 (8) 2418-2422.

Nebus, J., Costes, F., Wallo, W., and Miller, D., 2007: *Clinical Improvements in Facial Photoaging With Topical Treatments Containing Mushroom Extracts.* Poster presented at 65th Annual Meeting of the American Academy of Dermatology Washington, DC.

Nemtanu, M.R., Mineal, R., Mazliu, E., Setnic, S., Mitru, E., Balotescu, C., et al. *Effects of Ionizing Radiation on the Food Bioprocess Technol Antioxidant and Antimicrobial Activities of Sea Buckthorn Oil.* Acta Horticulture. 2009. 826; 255-260.

Nghiem, D.X., Kazimi, N., Clydesdale G., Ananthaswamy, H.N., Kripke, M.L., Ullrich, S.E. *Ultraviolet a Radiation Suppresses an Established Immune Response: Implications for Sunscreen Design.* J Invest Dermatol. 2001. 117 (5) 1193-1199.

Noel, A., and R.M., Tyrrell. *Development of Refractoriness of Induced Human Heme Oxygenase-1 Gene Expression to Reinduction by UVA Irradiation and Hemin.* Photochem Photobiol. 1997. 66 (4) 456-463.

Kanti Bhooshan Pandey and Syed Ibrahim Rizvi. *Plant Polyphenols as Dietary Antioxidants in Human Health and Disease.* Oxid Med Cell Longev. 2009. 2 (5) 270-278.

Parmar, J., Sharma, P., Verma, P., and Goyal, P.K. *Chemopreventive Action of Syzygium Cumini on DMBA-Induced Skin Papillomagenesis in Mice.* Asian Pacific Journal of Cancer Prevention. 2010. 11 (1) 261-265.

Parshad, R., et al. *Protective Action of Plant Polyphenols on Radiation-Induced Chromatid Breaks in Cultured Human Cells.* Anticancer Res. 1998. 18 (5A) 3263-3266.

Patel, C.A., Divakar, K., Santani, D., Solanki, H.K., and Thakkar, J.H. *Remedial Prospective of hippophae rhamnoides linn. (sea buckthorn).* ISRN Pharmacology 2012. 436857.

Perde-Schrepler, M., Chereches, G., Brie, I., Tatomir, C., Postescu, I.D., Soran, L., and Filip, A. *Grape Seed Extract as Photochemopreventive Agent against UVB-induced Skin Cancer*. J Photochem Photobio B. 2012. 118; 16-21.

Pinnell, Sheldon R.S.R. *Cutaneous Photodamage, Oxidative Stress, and Topical Antioxidant Protection.* Journal of the American Academy of Dermatology. 2003. 48 (1) 1-19; quiz 20-2.

Rabe J.H., Mamelak A.J., McElgunn, P.J., et al. *Photoaging: Mechanism and Repair.* J Am Acad Dermatol. 2006. 55 (1) 1-19.

Reszko, et al. *Cosmeceuticals: Practical Applications.* Dermatologic Clinics. 2009. 27 (4) 401-416.

Robak, J., and Gryglewski, R.J. *Flavonoids are Scavengers of Superoxide Anions.* Biochem Pharmacol. 1988. 37 (5) 837-841.

Rousi, A. *The Genus Hippophae L. A Taxonomic Study.* Annales Botanici Fennici. 1971. 8; 177-227.

Saha, R. *Cosmeceuticals and Herbal Drugs: Practical Uses.* IJPSR. 2012. 3 (1) 59.

Schwartz, E., Cruickshank, F.A., Christensen, C.C., et al. *Collagen Alterations in Chronically Sun-Damaged Human Skin.* Photochem Photobiol. 1993. 58 (6) 841-844.

Shi, X.L., et al. *Antioxidant Properties of (—)-epicatechin-3-gallate and Its Inhibition of Cr (VI)-induced DNA Damage and Cr (IV) - or TPA-stimulated NF-kappa B Activation.* Mol Cell Biochem. 2000. 206 (1-2) 125-132.

Sime, S., and Reeve, V.E. *Protection from Inflammation, Immunosuppression and Carcinogenesis Induced by UV Radiation in Mice by Topical Pycnogenol.* Photochem Photobiol. 2004. 79 (2) 193-198.

Siscovick, J.R., Zapolanski, T., Magro, C., Carrington, K., Prograis, S., Nussbaum, M., and Granstein, R.D. *Polypodium leucotomos Inhibits Ultraviolet B Radiation-Induced Immunosuppression.* Photodermatology, Photoimmunology & Photomedicine. 2008. 24 (3) 134-141.

Struthers, L., R., Patel, J., Clark, and S., Thomas. *Direct Detection of 8-oxodeoxyguanosine and 8-Oxoguanine by Avidin and Its Analogues.* Anal. Biochem. 1998. 255 (1) 20-31.

Sorg, O., Kuenzli, S., Kaya, G., et al. *Proposed Mechanisms of Action for Retinoid Derivatives in the Treatment of Skin Aging.* J Cosmet Dermatol. 2005. 4 (4) 237-244.

Spencer, J.P., Abd, El Mohsen M.M., Minihane A.M., and Mathers. *Biomarkers of the Intake of Dietary Polyphenols: Strengths, Limitations and Application in Nutrition Research*. Br J Nutr. 2008. 99 (1) 12-22.

Svobodová, Alena, A., Jitka Psotová J., and Daniela Walterová D. *Natural Phenolics in the Prevention of UV-Induced Skin Damage.* A Review. Biomedical Papers of the Medical Faculty of the University Palacký, Olomouc, Czechoslovakia. 2003. 147 (2) 137-145.

Talwar, H.S., Griffiths, C.E., Fisher, G.J., et al. *Reduced Type I and Type III Procollagens In Photodamaged Adult Human Skin*. J Invest Dermatol. 1995. 105 (2) 285-90.

Thring, Tamsyn S.A.T.S., Pauline, P. Hili and Declan, P.D.P. *Naughton. Anti-Collagenase, Anti-Elastase and Anti-Oxidant Activities of Extracts from 21 Plants.* BMC Complementary and Alternative Medicine. 2009. 9 (27) 1-11.

Torel, J., and Cillard, J. *Antioxidant Activity of Flavonoids and Reactivity with Peroxy Radical.* Phytochemistry. 1986. 25 (2) 383-385.

Tyrimou, N., 2012: *Skin Care Market Radiant for Foreseeable Future.* GC Magazine.

Unno, T., et al. *Electron spin Resonance Spectroscopic Evaluation of Scavenging Activity of Tea Catechins on Superoxide Radicals Generated by a Phenazine Methosulfate and NADH System.* Food Chem Toxicol. 2002. 7; 259-265.

Uttara, B., Singh, A.V., Zamboni, P., and Mahajan, R.T. *Oxidative Stress and Neurodegenerative Diseases: A Review of Upstream and Downstream Antioxidant Therapeutic Options.* Current Neuropharmacology. 2009. 7 (1) 65-74.

Varani, J., Warner, R.L., Gharaee-Kermani, Phan, S.H., Kang, S., Chung, J.H., et al. *Vitamin A Antagonizes Decreased Cell Growth and Elevated Collagen- Degrading Matrix Metalloproteinases and Stimulates Collagen Accumulation in Naturally Aged Human Skin.* Journal of Investigative Dermatology. 2000. 114 (3) 480-486.

Varila, E., et al. *The Effect of Topical Oestradiol on Skin Collagen of Postmenopausal Women*. Br J Obstet Gynaecol. 1995. 102 (12) 985-989.

Vinson, J.A., Dabbagh, Y.A., Serry M.M., et al. *Plant Flavonoids, Especially Tea Flavonols, is Powerful Antioxidants using an in Vitro Oxidation Model for Heart Disease.* J Agric Food Chem. 1995. 43 (11) 2800-2802.

Wagner, V.H., P., Diesel and M., Seitz. *Chemistry and Analysis of Silymarin from Silybum Marianum Gaertn*. Arzneimittelforschung. 1974. 24; 466-471.

Wang, Z.Y., et al. *Inhibitory Effects of Black Tea, Green Tea, Decaffeinated Black Tea, and Decaffeinated Green Tea on Ultraviolet B Light-induced Skin Carcinogenesis in 7, 12-dimethylbenz [a] anthracene-initiated SKH-1 Mice*. Cancer Res. 1994. 54 (13) 3428-3435.

Wang, Z.Y., et al. *Inhibitory Effect of Green Tea on the Growth of Established Skin Papillomas in Mice.* Cancer Res. 1992. 52 (23) 6657-6665.

Wang, Z.Y., Agarwal, R., Bickers, D.R., and Mukhtar, H. *Protection against Ultraviolet B Radiation-Induced Photocarcinogenesis in Hairless Mice by Green Tea Polyphenols*. Carcinogenesis. 1991. 12 (8) 1527-30.

Wei, H.C., et al. *Scavenging of Hydrogen Peroxide and Inhibition of Ultraviolet Light-Induced Oxidative DNA Damage by Aqueous Extracts from Green and Black Teas.* Free Radic Biol Med. 1999. 26 (11) 1427-1435.

Widyarini, S., et al. *Isoflavonoid Compounds from Red Clover (trifolium pratense) Protect From Inflammation and Immune Suppression Induced by UV Radiation.* Photochem Photobiol. 2001. 74 (3) 465-470.

Wiseman, H., et al. *Isoflavone Phytoestrogens Consumed in Soy Decrease F-2-isoprostane Concentrations and Increase Resistance of Low-Density Lipoprotein to Oxidation in Humans.* Am J Clin Nutr. 2000. 72 (2) 395-400.

Yang, C.S., Maliakal P., and Meng, X. *Inhibition of Carcinogenesis by Tea.* Annu Rev Pharmacol Toxicol. 2002. 42; 25-54.

Yang, B., R.M., Karlsson, P.M., Oksman and H.P., Kallio. *Phytosterols in Sea Buckthorn (Hippophae rhamnoides L.) Berries: Identification and Effects of Different Origins and Harvesting Time.* J Agric Food Chem. 2001. 49 (11) 5620-5629.

Yoshikawa, T., Rae, V., Bruins-Hot, W., Vander Berg, J.W., Taylor, J.R., Streilein, J W. *Susceptibility to the effects of UVB Radiation on Induction of Contact Hypersensitivity as a Risk Factor for Skin Cancer in Humans.* J Invest Dermatol. 1990. 95 (5) 530-536.

Zadernowski, R., et al. *Composition of Phenolic Acids in Sea Buckthorn (Hippophae Rhamnoides L.) Berries.* Journal of the American Oil Chemists' Society. 2005. 82 (3) 175-179.

L., Zhang, S., Lerner, W.V., Rustrum and G.A., Hofmann. *Electroporation-mediated Topical Delivery of Vitamin C for Cosmetic Applications.* Bioelectrochem Bioenerg. 1999. 48 (2) 453-461.

Zhang, W., J., Yang, J., Duo, B., Ren and J., Guo, 1989: *Preliminary Study of Biochemical Constitutions of Berry of Sea Buckthorn Growing in Shanxi Province and Their Changing Trend.* Proceedings of International Symposium on Sea Buckthorn (H. Rhamnoides L.), Xian, China. 129-132.