bend
BEAUTY

THE ULTIMATE GUIDE TO SKIN HEALTH & LONGEVITY

Section 2

# More than Skin Deep:
## The Latest Science of Skin Health & Aging

Nancy L Morse, BSc. (Hons), CNPA

## NOTICE TO READER

This book is not intended to provide medical advice or to take the place of medical advice and treatment from your personal physician. Readers are advised to consult their doctors or qualified health professionals regarding specific health questions. Neither the publisher nor the author takes responsibility for the possible health consequences of any person reading or following the information in this book. All readers, especially those taking prescription or over-the-counter medications, should consult their physicians before beginning any nutrition or supplement program.

† **These statements have not been evaluated by the Food and Drug Administration. This book is not intended to diagnose, treat, cure or prevent any disease.**

# About this eBook Series

*This series is divided into three separate sections to make it easier to enjoy.*

Section 1

## How Diet, Lifestyle, and the Environment Impact Your Skin

Focuses on skin health and longevity, and what influences both.

Section 2

## More than Skin Deep: The Latest Science of Skin Health & Aging

Describes what your skin reveals about your health, and how it impacts your health.

Section 3

## The Top Foods and Nutraceuticals to Benefit Skin Health & Longevity

Presents the clinical research supporting the benefits of our favorite foods and supplements to maintain your skin health and longevity.

# Orientation

## *What did you learn in Section 1?*

Your skin performs many functions that are important to your overall health. It provides a protective chemical and physical barrier between you and the outside world, helps you interact with your environment, makes vitamin D and is part of your body's total antioxidant defense and detoxifying systems. Many factors impact how well your skin can do its job including:

- Your specific Skin Climate® that is partly governed by your unique genetic make-up
- Environmental factors including your diet and lifestyle
- Your level of exposure to:
  - Pollution/environmental toxins
  - UV radiation from sunlight

Most of the factors that negatively impact your skin's function, either contribute to the amount of toxins within your body or prevent you from eliminating them through your internal detoxifying systems. These factors not only contribute to signs of skin aging including thinning, discoloration, wrinkles, and dryness; they also adversely impact how the rest of your body functions. Over time, they either contribute to the start or to continued progression of metabolic syndrome, and age-related diseases including CVD, arthritis, type 2 diabetes, AD, and cancer. All these conditions decrease your longevity.

Your body seeks to maintain homeostasis (balance/stability). Mild, short-lived forms of stress can improve skin health and longevity by stimulating your antioxidant enzyme production, detoxification, and healthy cell survival mechanisms. Some examples of mild stressors include:

- Calorie restriction
- Moderate exercise
- Pleasing and exciting life events

However, excess, and long-term stress by various factors can have the opposite effect. Your body works best when a proper balance is maintained. Additional examples where balance is particularly important include:

- Omega-3/6 fatty acid intake
- Electrolyte and fluid intake
- Gut microbiome composition

### *Maintaining your healthy skin and longevity is a lot about maintaining proper balance!*

When balance is disturbed by too many negative factors, you can take steps to restore it by choosing appropriate foods and supplements.

### *What is next on your agenda?*

In Section 2 you will find out:

- How skin health is connected to health in other areas of your body
- What your skin condition can tell you about how other parts of your body are functioning
- How the health of other body systems can impact skin health
- How skin health can impact the health of other body systems

# Table of Contents

## *Section 2*

### *Part 4.0: Skin Health: Let's Dig Deeper*



## *Conclusion*

4.0

# Skin Health: Let's Dig Deeper

*What does your skin reveal about your health & how does your skin impact your health?*

If by now, you have come to realize that your Skin Climate® can impact your health, AND that your skin can also tell you a lot about what ails you, you would be right! The type of skin you are in can both influence your well-being, and help you discover what health problems you have! So, let us examine those two things more closely.

## How does your Skin Impact your Health?

**Your skin:**

- Is part of your immune system. In that capacity, it forms a defensive barrier against external pathogens.
- Is your second most important detoxifying organ, next to liver. In that capacity:
  - It gets rid of internally produced bioactive waste substances, lipids, and cholesterol by secreting them in sweat and sebum.
  - It destroys or neutralizes the harmful effects of externally derived xenobiotics including heavy metals, drugs, environmental pollutants, cosmetics, and dietary components such as food additives and synthetic supplements by[1]:
    - Inactivating and neutralizing them – which unfortunately makes even more ROS
    - Making internal antioxidant enzymes to scavenge those ROS, plus ones that are formed by sunlight hitting your skin.

  In doing so, your skin prevents you from being exposed to these harmful ROS that contribute to inflammaging. Inflammaging promotes both skin aging and various age-related diseases (1-5) that reduce your longevity.

In essence your skin helps you regain balance following exposure to many and diverse stressors.

However, if your Skin Climate® has been altered to an inflammatory state by various factors or is not satisfactorily nourished, it cannot carry out its essential immune and detoxifying roles. That can contribute to your deteriorating health. On the other hand, if you look after your skin and maintain normal/healthy Skin Climate®, it will look after you!

## What does your Skin reveal about your Health?

Your skin is like the canary in the coal mine. It can look and feel different if something is not right in another part of your body. For example:

- Skin changes including rashes and itching, flushing, hyperpigmentation, spider veins, and yellowing are early warning signs of alcohol abuse[6] and reduced liver function[7]
- Facial wrinkling in smokers can indicate their susceptibility to COPD[8]
- Redness and swelling characteristic of inflammation can accompany gastrointestinal disorders[9, 10].

## So, pay attention to your skin. It could be trying to save you!

## PRO TIP

**GOOD TO KNOW:** According to the American Academy of Dermatology, skin changes, including rashes, growths, discoloration, and texture differences, can indicate serious health problems[11]. On the other hand, fewer skin wrinkles are often associated with lower blood pressure, a lower risk of heart disease and stroke, and longer life expectancy[12]!

## 4.1 The Gut-Skin Axis

Your skin, much like your gut/intestinal tract, is an integral part of your immune system. Both:

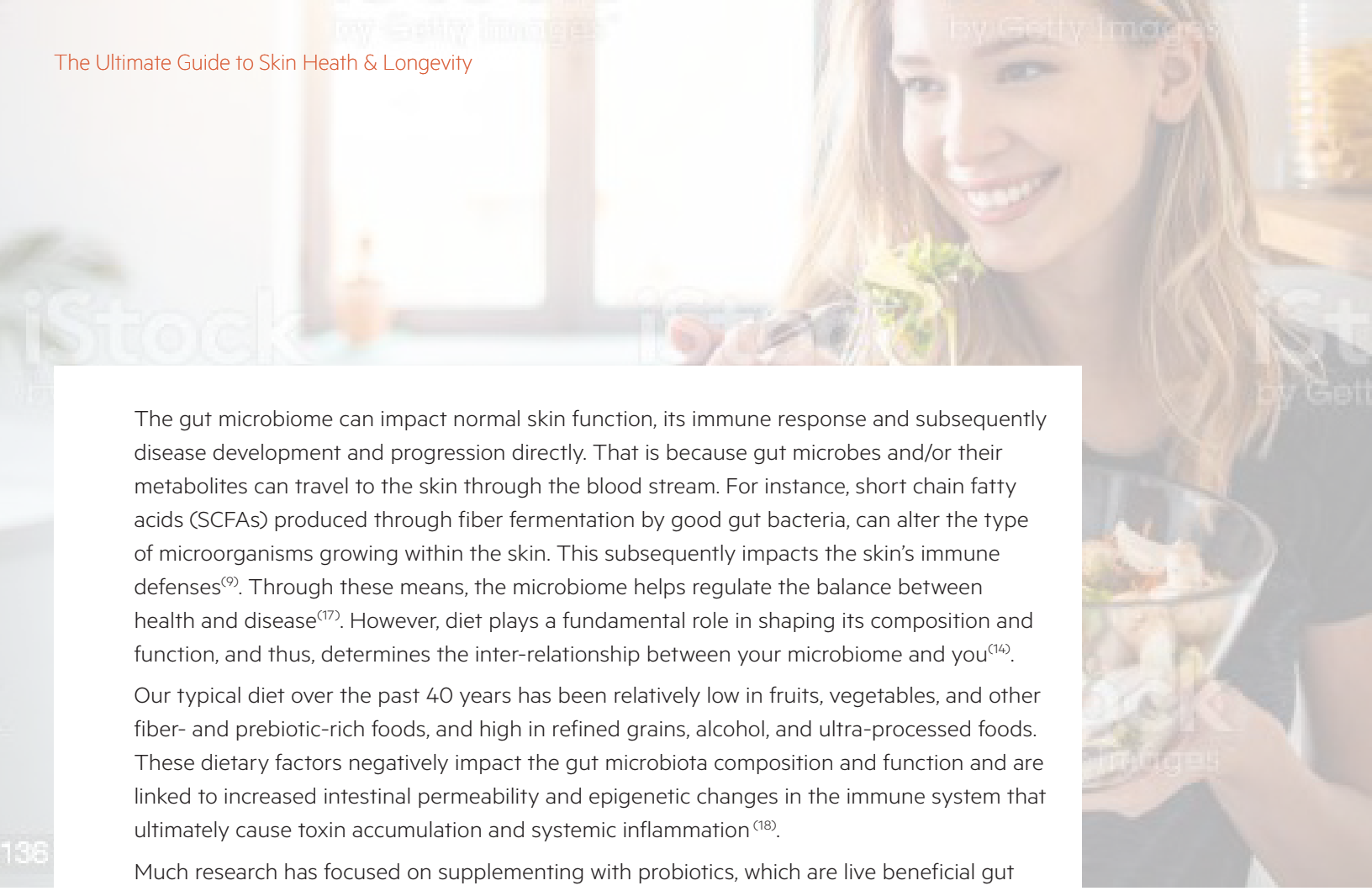
- Form a defensive barrier that protects you against external pathogens
- Are essential to homeostasis
- Help regain that balance following damage by various stressors.

Many studies link gut health to immune and hormone functions within skin, and gastrointestinal disorders are often accompanied by visual skin changes[9, 10], including redness and swelling characteristic of inflammation. In fact, 14% of patients with ulcerative colitis, 24% of people with Crohn's disease, and 25% of those with celiac disease, also have skin problems, and psoriasis is more common in patients with Crohn's disease than in healthy people[10]. This intricate connection between the gut and skin has led to the term "Gut-Skin Axis", and increasingly skin symptoms associated with abnormal gut microbiome are being reported[13].

The gut microbiome is a diverse array of micro-organisms including bacteria, fungi, protozoa, and viruses that reside mostly in our intestines, where they maintain a symbiotic relationship with us[9] and enormously impact our health[14]. Negative changes in its composition and function, termed dysbiosis, are linked to altered immune response, and the development of skin diseases, including atopic dermatitis[13, 15]. On the other hand, a healthy human microbiome can:

- Produce many nutrients important for human health
- Prevent infections
- Beneficially influence immune response
- Enhance human metabolism
- Regulate the balance between health and disease

That is because nutrients and other bioactive substances made by our residing microbiota, are skin and whole body accessible[16]. Discovery of this connection led to the idea that improving our microbiome can play a role in skin disease prevention and treatment[16], and overall health and longevity.



The gut microbiome can impact normal skin function, its immune response and subsequently disease development and progression directly. That is because gut microbes and/or their metabolites can travel to the skin through the blood stream. For instance, short chain fatty acids (SCFAs) produced through fiber fermentation by good gut bacteria, can alter the type of microorganisms growing within the skin. This subsequently impacts the skin's immune defenses[9]. Through these means, the microbiome helps regulate the balance between health and disease[17]. However, diet plays a fundamental role in shaping its composition and function, and thus, determines the inter-relationship between your microbiome and you[14].

Our typical diet over the past 40 years has been relatively low in fruits, vegetables, and other fiber- and prebiotic-rich foods, and high in refined grains, alcohol, and ultra-processed foods. These dietary factors negatively impact the gut microbiota composition and function and are linked to increased intestinal permeability and epigenetic changes in the immune system that ultimately cause toxin accumulation and systemic inflammation[18].

Much research has focused on supplementing with probiotics, which are live beneficial gut bacteria found in yogurt, fermented vegetables, and sold as supplements. However, your diet impacts their effectiveness, because the food you eat is also the food they need to survive and flourish. This is where prebiotics become important. Prebiotics are dietary fibers that we cannot or only partly digest. They instead remain within the digestive tract where they become food for beneficial bacteria. Therefore, combining prebiotic[14] and probiotic supplementation might be the best approach to manipulate microbiome composition[15] essential to maximize beneficial effects.

In essence, ensuring you have a healthy microbiome helps maintain a healthy Skin Climate® by nourishing your skin from within through the "Gut-Skin Axis".

## Ongoing Research

Research on how the human gut microbiome impacts our response to the foods and supplements we eat, shows we can harness its potential[19] through our diet, so we can prevent or treat a variety of skin conditions, including AD, psoriasis, and acne[20]. This microbiome manipulation to achieve, maintain or restore favourable gastrointestinal health is also necessary to maintain and improve our overall health[17] and longevity. The ongoing Australian Research Council Longevity Intervention study is the first to investigate this association, among other things[21].

## 4.2 The Liver-Skin Axis

Your liver helps maintain your nutrient and hormone balance and plays a significant role in xenobiotic detoxification [22]. Its main job is to filter blood coming from the digestive tract to obtain nutrients including carbohydrates, fats, and proteins. It converts blood sugar to glycogen that is used to make energy, makes amino acids required for protein formation and makes bile that is secreted into the small intestine where it helps break down and process dietary fat. It also stores vitamins and minerals and breaks down hormones so they can be eliminated, thereby maintaining hormonal balance. In addition, the liver removes toxins and waste products from the blood, detoxifies chemicals and metabolizes drugs that are secreted into bile for elimination [23].

Liver function is influenced by both nutrients within our diet and environmental toxins:

- Nutrients: Diet effects liver enzyme function, even in healthy people. For example, high carbohydrate, in particular sugar laden diets, can significantly increase certain liver enzymes and blood fats [24], which contributes to liver stress.
- Toxin overload from our food, water, and the air we breathe, can lead to a congested and overtaxed liver, and build-up of toxins within us. Exposure to environmental toxins such as heavy metals (e.g., lead and mercury) and polychlorinated biphenyls (PCBs) increase liver enzymes associated with liver injury that can lead to development of liver disease including non-alcoholic fatty liver disease (NAFLD) [25].

Poor liver function can lead to overall changes in body physiology, including toxin build-up and reduced ability to metabolize nutrients. This also reduces nutrient supply to the skin, while toxins simultaneously accumulate there. Consequently, symptoms of reduced liver function often first appear in the skin [7] In fact, skin keratinocytes grown in cell culture, are sometimes used to detect liver injury [26]. Skin abnormalities that may indicate poor liver function include [7]:

- Irritation and itching
- Crusty nodules
- Irregularly shaped, pale patches on the arms and legs caused by pigment loss (Bier spots)
- Spider veins and scattered, needle-thin superficial capillaries
- Crimson coloration in the palms and fingertips
- Excessive bleeding and bruising
- Hyperpigmentation/brown liver spots, which project an older appearance
- Hair and nail loss
- Yellowing appearance associated with jaundice

This connection between liver function and skin health has led to the term “Liver-Skin Axis” [27].

Various foods and supplements can impact skin through the liver-skin axis. For example, sulforaphane derived from cruciferous vegetables can reduce liver stress related to environmental toxins, and silymarin derived from milk thistle helps to modify liver insult partly attributed to poor diet.

## 4.3 The Brain-Skin Axis

The "brain-skin axis" clarifies a link between skin condition and mental state. For example, itchy skin is often a pervasive feature of psychiatric disorders including obsessive compulsive disorders, depression [28], and psoriasis [29]. This itchiness is often responsible for increased anxiety and negative feelings, decreased self-esteem and quality of life, and even for increased death [29].

In recent decades, a relatively new field of medicine called Psycho-dermatology has been developed to address the complex interaction between the skin and mind. Treatment of psycho-dermatological disorders focuses on improving function, reducing physical distress, diagnosing, and treating depression and anxiety associated with skin disease, managing social isolation, and improving patient self-esteem. Both pharmacological and psychological treatments are used to address such disorders.

Some clinicians feel that psycho-dermatology is unnecessary because current medical practices already take a holistic approach to treating patients [30]. However, patients with psycho-dermatologic disorders frequently resist referral to mental health professionals[31]. As a result, they never really get the help they need to address all their symptoms that are related through the "Brain-Skin Axis". Therefore, foods and supplements that combine direct skin related therapeutic benefits with mood/motivation enhancing and stress reducing effects may be just what the doctor ordered! And they may provide a bonus of enhanced longevity because happy people live longer, healthy lives.

The English Longitudinal Study of Aging showed that personal well-being is associated with greater survival. Other studies report that happier older people are less likely to develop daily living activity declines, have better recoveries in motor, cognitive, and functional performance after a heart attack or stroke, and happiness is linked with reduced death risk in both healthy and ill populations [34].

Our brain and nerve functions are two of the many factors that impact our ability to repair cell and tissue damage that accumulates throughout our lives [35]. Therefore, it is not surprising that happy people, whose brains are functioning well, live longer.

# PRO TIP

**GOOD TO KNOW:**

Most of your "happy hormone", serotonin, is made in your gut? So, your gut communicates directly with your brain through the Gut-Brain Axis, and your brain communicates directly with your skin through the Brain-Skin Axis. That interconnection of body systems has led to another concept coined the "Gut–Brain–Skin Axis", where your microbiome can both impact your stress response and your skin's response to that stress[32, 33].

## 4.4 Healthy Aging

### Aging is an unavoidable, age-dependent gradual failure of homeostasis that occurs at molecular, subcellular, cellular, tissue, and whole-body levels [36], and is a critical risk factor for several age-related disorders [37].

Even though our population life expectancy is continuously rising, our healthspan, defined as the years of healthy life, is not [34]. This highlights the need for strategies that promote longevity combined with healthy aging to ensure a good quality of life as we age [38].

#### 4.4.1 What is Aging?

Aging is an inevitable and integral part of our lives. It involves many physiological, metabolic, hormonal, immune and neurocognitive changes that collectively contribute to the development of age-related metabolic disease and physical disabilities over time [39].

#### 4.4.2 How and why do we Age?

Aging involves similar processes in most living species that occur in response to accumulated “damage” that happens throughout life. These processes are known as the Hallmarks of Aging [18, 34]. Your life, and quality of life, progresses depending on how these processes evolve. Different scientists define these processes in different ways, but they essentially include:

- Genomic instability (DNA damage and functional loss)
- Telomere attrition (erosion/slow destruction)
- Epigenetic changes
- Loss of proteostasis
- Mitochondrial dysfunction
- Deregulated nutrient sensing and metabolism
- Cellular senescence
- Stem cell exhaustion
- Altered intercellular communication (cell signaling)

Many of these have been addressed in other parts of this book, so this section will focus only on certain significant aspects or contributors not already discussed.

Among these aging processes, telomere attrition is the primary hallmark that determines how long we will live [34].

**PRO TIP**

**GOOD TO KNOW:**

**DNA damage includes nonfunctional bonds and epigenetic "sludge", that accumulates, leading to DNA instability and dysfunction, cell stress, and premature aging. Changes to reduce this damage & potentially increase health and longevity include:**

- Positive behavior modifications
- Limiting harmful environmental exposures
- Maintaining a healthy body weight
- Ensuring adequate restful sleep
- Exercising moderately
- Adherence to a Mediterranean diet
- Supplements including antioxidants (e.g., beta-carotene, vitamins C and E), omega-3 fatty acids [40] and others

Genetic and epigenetic factors may play a bigger role the older we get, while environmental and lifestyle factors play a pivotal role during youth [38]. However, all these factors are connected because stress caused by environmental factors, leads to the accumulation of accidental metabolic errors and abnormalities, increases free radical and ROS

production, and macromolecular damage, at both cellular and tissue levels as we progress through life.

We have already learned that:

- Minor stress can prevent or eliminate genetic errors and increase expression of genes responsible for stress-resistance, which boosts stress coping capacity and slows aging.

On the other hand:

- Prolonged or severe stress exposure exhausts our defense mechanisms, causing drastic accumulation of errors and physiological abnormalities, which accelerates the aging process [36].

So, healthy aging is partly about getting the right balance of stress throughout life.

The other part is about preserving body repair mechanisms.

During aging, cellular quality control activities become dysfunctional. These include processes like proteostasis and autophagy, which remove misfolded/damaged proteins and dysfunctional organelles, respectively. When dysfunction happens, the body loses its capacity to repair any accumulated damage. Therefore, our initial resiliency against stress factors that contribute to this damage, PLUS how well we can repair damage that has occurred, dictate how well we will age.

Factors that impact our ability to repair damage include our genetic predisposition, stress response system, brain and nerve function, immune response, etc. [35]. However, that capacity to repair damage can be enhanced through various means including dietary modification and supplement use.

Let's look at some of the things involved with deterioration, repair and survival.

### 4.4.3 Loss of proteostasis

In Part 3.3.2.1, Exercise, we learned how important proteins are to maintain our lean body mass to enhance longevity. Here we are talking about how proteins impact cell longevity.

Proteostasis is the process that regulates proteins within cells to maintain their health, which ultimately impacts the health of the whole person. It includes protein specific quality control functions such as biosynthesis, folding, trafficking, and degrading and eliminating damaged proteins [3].

During aging, proteins become damaged through oxidation, and bonds form indiscriminately between fibers, causing them to tangle/clump and become toxic to cells. On top of that, the functional capacity of the quality control machinery declines, which allows these damaged proteins to accumulate [3]. If left unchecked, they can contribute to loss of cell function leading to senescence or cell death.

### 4.4.4 Autophagy

Autophagy is nature's way of ridding our bodies of damaged cells and/or cell parts. It is an important cellular recycling process needed to remodel cellular contents, and to safeguard against accumulation of damaged and tangled/clumped biomolecules. Its activity is increased under stressful conditions such as oxidative stress [41]. A similar process called mitophagy does the same thing specifically within mitochondria, which also helps to save energy. Both autophagy and mitophagy are part of the cell's response to free radicals and mitochondrial dysfunction [42].

Autophagy systematically degrades and recycles damaged organelles and cell membranes. It is particularly important to control protein degradation and recycling because excessive protein biosynthesis and accumulation of misplaced and misfolded proteins is toxic for cells. It leads to stress, which in turn diminishes synthesis of healthy and normal proteins (i.e., your enzymes), which are needed to perform all metabolic processes. Therefore, normal functioning autophagy is critical for overall normal cell and whole person function.

Autophagy is performed by specialized enzymes that collectively clean up cellular debris, but their capacity to fulfill their roles diminishes with age. However, improving their function, contributes to longevity [36].

Age-suppressed autophagy can be reactivated by calorie restriction [43]. For example, subjects who maintained a calorie restricted diet for 3-15 years, had less inflammation, and increased levels of autophagy regulators that improved their protein quality control processes and enhanced removal of dysfunctional proteins and organelles [44].

But autophagy does more than just repair/recycle damaged organelles, cell membranes and proteins. It also helps [45]:

- Survive starvation by recycling unneeded proteins to those essential for survival
- Degrade infectious agents (i.e., bacteria and viruses), which prevents infection
- Initiate programmed cell death – Currently it is unclear whether autophagy activity in dying cells is the cause of death or is instead a survival mechanism in an attempt to prevent it. In any event, this type of programmed cell death ultimately serves the same function as apoptosis, although perhaps on a larger scale. Where apoptosis destroys cells before they become cancerous, programmed cell death associated with autophagy may occur within a tumor setting, where larger quantities of biological material must be destroyed and recycled to sustain life [46].

Autophagy failures may be the main reason for damaged cell accumulation and aging [47]. Defects in autophagy have been linked to various human diseases, including neurodegeneration and cancer, and interest in modulating autophagy to treat these diseases has grown rapidly [45].

However, autophagy is another one of these double-edged swords. It can both protect against cancer as well as potentially contribute to it growth depending on various factors [45]. Interestingly, regulators of inflammation, also control autophagy, and form a network that is critical for normal tissue functions. However, this co-operative network is dysregulated in cancer cells [48]. Therefore, stimulating autophagy in normal healthy cells is beneficial but stimulating it in cancer cells is not.

### 4.4.5 Chronic systemic inflammation – Inflammaging

The mechanism whereby chronic systemic inflammation develops is described in Part 3.3.3 Pollution/environmental toxins. Here we will look at how it relates to aging.

In recent years, the incidence of diseases associated with chronic systemic inflammation has increased dramatically for all age groups of people living in industrialized countries who follow a Western lifestyle. However, those disease rates are relatively low among non-Westernized populations, where diets, lifestyles and ecological niches resemble those of our ancestors.

Chronic systemic inflammation can be induced by poor diet and lifestyle habits, and pollutants that can increase oxidative stress, alter cell communication, and cause DNA changes. These non-heritable, environmental factors were found to be the strongest contributors to differences in chronic inflammation in a study, including 210 healthy twins between 8 and 82 years old. It showed that lifelong exposure to such physical, chemical, and biological stresses, from the prenatal period onward, are the main drivers of chronic systemic inflammation [18].

Chronic systemic inflammation that develops with advanced age is sometimes also referred to as "Inflammaging". It is thought to accelerate the aging process and worsen many age-related diseases. It occurs in the absence of infection, is instead primarily driven by internal signals, and includes increased levels of blood inflammatory markers [49].

Most older people develop inflammaging, which makes them highly susceptibility to chronic diseases, disability, frailty, and premature death. Factors that influence inflammaging include genetic susceptibility, central obesity, increased gut permeability, microbiome changes, cellular senescence, inflammation, oxidative stress caused by dysfunctional mitochondria, immune cell dysregulation, chronic infections [50], overnutrition [51], and chronic stress occurring in any stage of an individual's life [52]. It causes CVDs and is also a risk factor for chronic kidney disease, diabetes, cancer, depression, dementia, and sarcopenia [50].

Inflammaging can develop following accumulation of misplaced and misfolded internally derived proteins or mitochondrial DNA within cells [53]. These damaged molecules are identified by immune cells as being problematic (i.e., they are not healthy or normal and so should be destroyed). This causes the immune cells to start an inflammatory response.

In addition, as we age our immune system function declines, triggering a cascade of events [54, 55], which causes low-grade chronic inflammation to development [49]. This process can occur in many tissues, and has been well-researched in fat tissue, so I will use it as an example of what happens at the tissue level.

As we age, white adipose/fat tissue accumulates around our middle, is deposited in other tissues that typically do not contain significant amounts of fat, and the fat stored on our hips and thighs tends to disappear. Simultaneously it is infiltrated by inflammatory cells that secret increased levels of inflammatory substances, while its anti-inflammatory activities become subdued. In addition, formation of new fat cells declines, oxidative stress and mitochondrial dysfunction increases, blood vessel formation decreases causing low oxygen supply, and fibrosis and senescent cells accumulate [56].

Senescent cells are notorious contributors of inflammatory substances to our aging body that is trying so hard to maintain homeostasis.

### 4.4.6 Telomere attrition

Chronic systemic inflammation has the potential to shorten your life by shortening your telomeres [57] Telomeres are the protective "caps" located at each end of your chromosomes that protect the integrity of your unique information-carrying DNA [58].

Every time your cells divide, their telomeres shorten until eventually they lose their ability to divide. This inability to divide hampers tissue repair and is associated with cell death. Thus, telomere length is a marker for aging [59].

However, successive cell replication is not the only reason why telomeres shorten. They also shorten in response

to intrinsic and extrinsic stress. In this capacity, telomeres function as stress sensors, where their shortening limits replication of cells that have accumulated significant damage. These cells then undergo senescence, rather than dying [60].

## PRO TIP

**EXPLAINED**

**Telomeres** keep your DNA from unraveling and fraying. Think of them like the plastic tips at the end of shoelaces. Each time DNA replicates, the telomeres get shorter. Once they are gone, the DNA unravels, and the cell dies.

In any event, longer telomeres within white blood cells and skeletal muscle cells are associated with healthy living, while shorter telomeres are found in those with age-related diseases, including cancer, CVD, obesity, diabetes, chronic pain, and stress [58].

Although our telomeres slowly shorten over time as we age, the rate at which this process occurs can be increased by inflammation and oxidative stress, and this, increases both the development of chronic age-related diseases and the rate of aging [57]. However, telomeres are also sensitive to variations in positive stress levels, mindset, and lifestyle, and their rescue may be sufficient to restore our cell viability [34] and promote our longevity.

The enzyme in human cells that is responsible for rebuilding telomeres is called telomerase. Many factors influence its activity including lifestyle and diet, and human studies show that beneficial modifications over time can significantly increase telomere length [61]. Therefore, we should be able to directly influence our telomere metabolism, slow their deterioration, and diminish our aging and perhaps extend our life and healthspan [62] by making positive dietary and lifestyle changes.

### 4.4.7 Cellular senescence

Senescence or biological aging is the gradual and inevitable deterioration of function. It is the fate of all multicellular organisms including us. However, it can be delayed. The word senescence can refer either to cellular senescence or the entire organism. Here, we will be exploring what happens in the cell. But keep in mind that if it happens in enough of your cells, it will also be happening to you as a whole person.

Senescence is induced when telomeres shorten [60]. It is irreversible cell growth arrest that can happen in response to various cellular stressors including oxidative stress, DNA damage, harmful somatic mutations, activation of oncogenes, cell-cell fusion and telomere erosion.

Senescent cell numbers increase as we age. These cells are resistant to apoptosis and can cause local and systemic dysfunction [63], because they are still alive, but they do not perform normally. They cannot replicate and have dramatic changes in shape and structure, gene expression, metabolism, epigenetic, and other functions [60]. Typically, they secrete a distinct profile of a pro-inflammatory substances that impact the function of neighboring cells. Over time, accumulation of such senescent cells can in turn induce senescence in adjacent young cells, thereby contributing to tissue dysfunction and even tumor formation [60]. It can also promote many chronic health conditions and diseases, including insulin resistance, CVD, pulmonary arterial hypertension, COPD, emphysema, AD, Parkinson's disease, macular degeneration, osteoarthritis, and cancer [18].

How senescent cells develop this pro-inflammatory state is not well understood but may include a combination of both internal and external social, environmental and lifestyle factors. The known internal factors include DNA damage, dysfunctional telomeres, epigenetic changes, and oxidative stress. The external contributors may include chronic infections, lifestyle-induced obesity, microbiome dysbiosis, poor diet, social and cultural changes, and environmental toxins [18].

Senescent cells can be either good or bad. They are beneficial during embryonic development, wound healing, and tissue repair. In addition, as a protective mechanism, cells can revert to a senescent state rather than becoming cancerous. On the other hand, senescent cells have been detected in many age-related diseases and in a variety of different tissues during aging, where they are believed to play a negative role [60, 64].

Various immune cells play a major role in killing and clearing senescent cells. However, immune system aging diminishes that capacity, which allows progressive build-up of senescent cells within body tissues over time [65], thereby contributing to the development of age-related diseases [64].

### 4.4.8 Stem cell exhaustion

In Part 2.1 Skin Structure, we learned about the role of stem cells in skin. Stem cells are those having the potential to develop into many different types of cells within your body. They exist in both embryonic and adult tissue and in the latter case, help to repair damaged tissue by replacing dead or dying cells, and play a vital role in maintaining tissue homeostasis as we age [66, 67].

Stem cell exhaustion is the decline in both stem cell numbers and their function. It occurs in virtually all tissues and organs maintained by adult stem cells, including the skin, forebrain, bone, muscle, and tissue involved in immune cell differentiation [67].

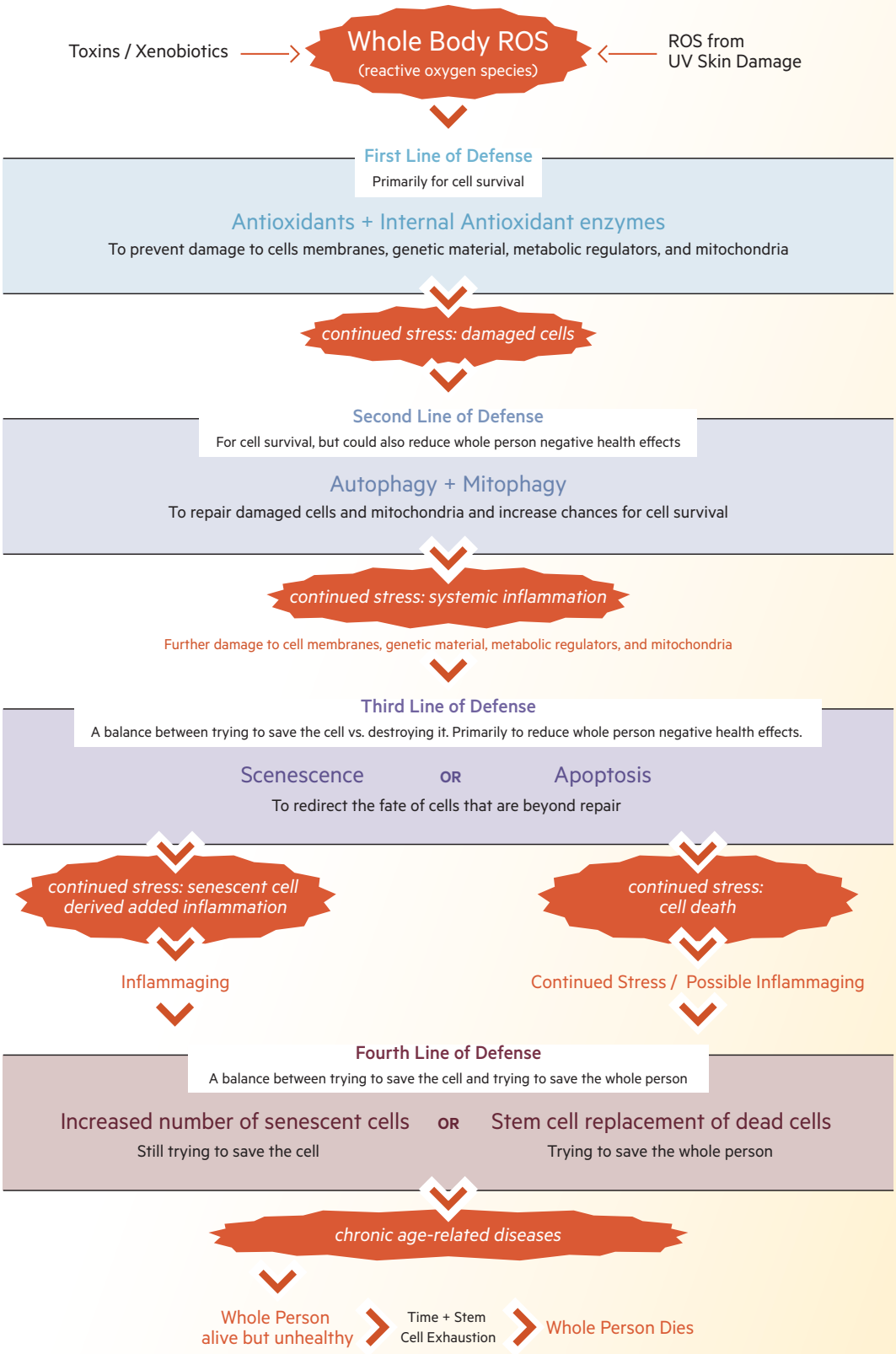
Stem cell exhaustion frequently occurs in age-related diseases and is one of the most significant hallmarks of aging [67], next to telomere attrition.

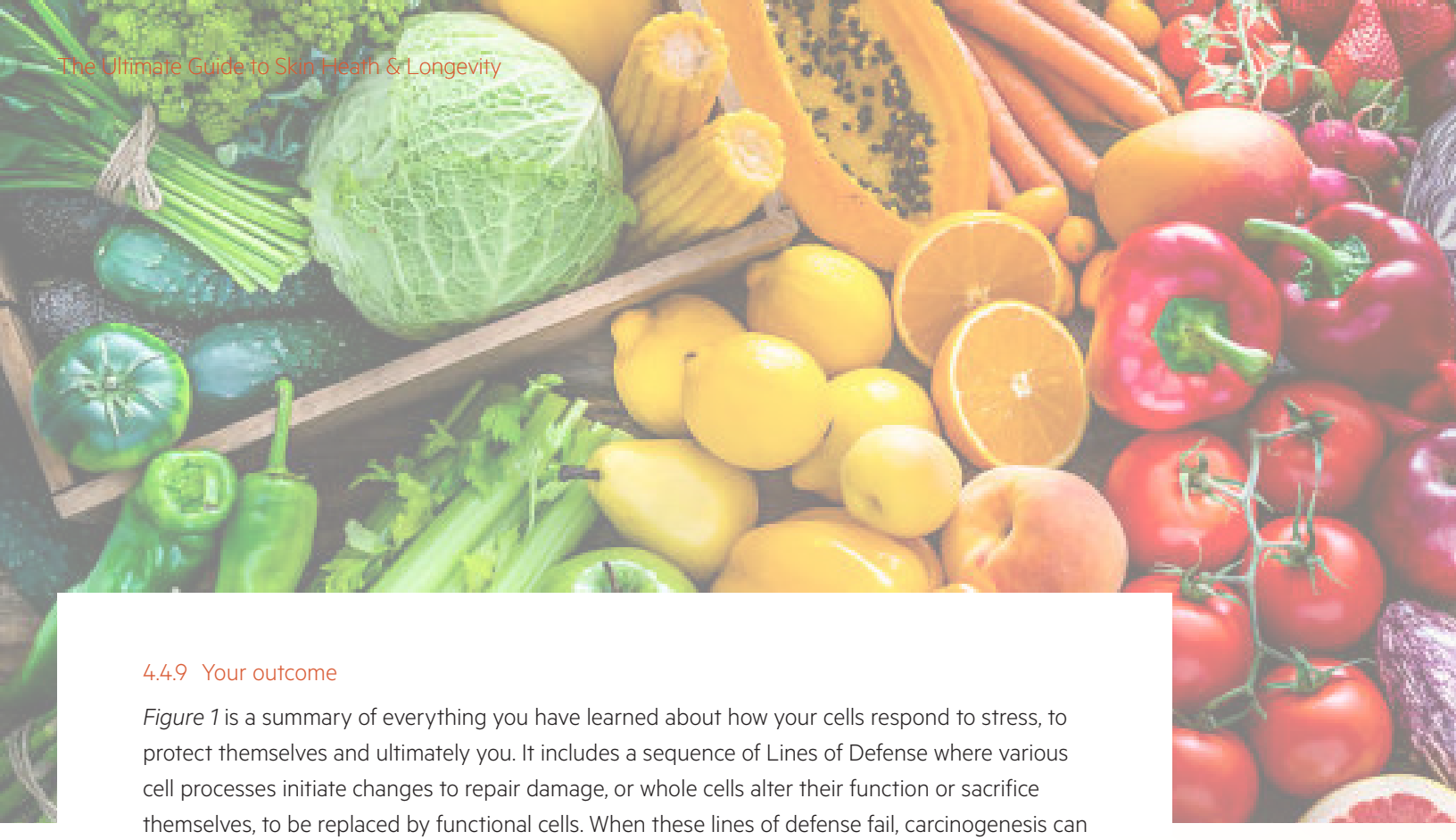
Our aging might partly arise from the inability of some stem cell types to continue to replenish tissues with specialized cells. In this regard, aging may not just be a matter of increased irreparable damage within cells and their resulting senescence or death. It could also include failure to replace damaged or dying cells with fully functioning cells because of dropping stem cell numbers over time [66].

This could have some obvious ramifications in aging, particularly in skin. As mentioned previously, our basement membrane contains stem cells needed for continuous epidermal regeneration [59]. Failure of stems cell to generate functioning epidermal cells can interfere in your ability to maintain an effective epidermal barrier. In addition, both hair growth and pigmentation are impacted by stem cell function. For example, in aging hair follicles, stem cells have diminished self-renewing capacity/they are exhausted, and this contributes to hair greying and hair loss [68, 69].

Stem cell aging and exhaustion are also important drivers of whole-body aging. Factors that can impact stem cell exhaustion include genetic predisposition, epigenetic, metabolic, and nutrient changes, and challenges to their homeostasis including circadian rhythm interruptions, too much exercise, and insufficient sleep. Accumulation of these negative stressors can significantly contribute to dysfunction and decline of adult stem cells during aging by impacting proteostasis, autophagy, inflammaging, telomere attrition and cellular senescence [67].

**Figure 1: The journey through an unhealthy life**





### 4.4.9 Your outcome

*Figure 1* is a summary of everything you have learned about how your cells respond to stress, to protect themselves and ultimately you. It includes a sequence of Lines of Defense where various cell processes initiate changes to repair damage, or whole cells alter their function or sacrifice themselves, to be replaced by functional cells. When these lines of defense fail, carcinogenesis can occur anywhere along the route. Keep in mind, that throughout this process, progressing from the top of the pathway and continuing to the bottom:

- Telomere attrition is occurring
- Tregs are accumulating. These modified lymphocytes can contribute to development of autoimmune disorders.
- Stem cell exhaustion is occurring.

## Your health, life and longevity are very much a balance between your cells' survival or death along this pathway.

**You have the power to alter your life path by shifting your lifestyle, and dietary foods and supplements intake towards achieving a metabolic state that:**

- Maximizes the beneficial features of some of the above-mentioned mechanisms (i.e., proteostasis, mitophagy, autophagy, stem cell regeneration)

**And**

- Minimizes the detrimental impact of others (i.e., inflammaging, telomere attrition, cellular senescence, stem cell exhaustion)

**Doing so, may protect your genetic material, mitochondria, and metabolic regulators, thereby preserving your cells. This ultimately impacts your skin aging and longevity.**

## How will you positively impact your skin, health, life and longevity?

brought to you by:

bend BEAUTY

# Conclusion

***What did you learn in Section 2?***

Your Skin Climate® can impact your health. If you have a normal/healthy Skin Climate®, your skin can help you regain homeostasis following exposure to many and diverse stressors. However, if your skin has been damaged by various factors or is not satisfactorily nourished, it changes your Skin Climate® to one that is pro-inflammatory. As a result, it cannot carry out its essential detoxifying and immune enhancing function. That can contribute to your deteriorating health. On the other hand, if you look after your skin, it will look after you. It can sometimes tell you that something is not right in another part of your body by developing some characteristic symptoms.

Your gut-skin axis, liver-skin axis, and brain-skin axis are pathways through which these organs communicate with one another via regulatory or metabolic processes, to perform their respective functions. Through these means, the operational capacity of one can impact that of the other, and vice versa. In addition, sometimes enhancing health of one is necessary to correct a problem in the other.

Aging is partly an imbalance between lifetime exposure to stressors and your ability to repair the damage they cause [70]. Your healthy aging depends on:

- Your initial resiliency against stress factors that contribute to cell and tissue damage
- How well you can repair damage that has occurred

The processes that impact damage recovery, can be modified through lifestyle and dietary changes to approach a metabolic state that balances between:

- Maximizing normal cell and tissue repair, and preservation through proteostasis, autophagy, and stem cell renewal

AND

- Minimizing cell and tissue loss attributed to senescence, cell death, and/or carcinogenesis.

When the balance is shifted towards cell and tissue loss, you can take further steps to repair and restore the damage by choosing appropriate foods and supplements.

## In Section 3:

**The Top Foods and Nutraceuticals to Benefit Skin Health & Longevity, will tell you:**

1. Which foods and supplements can support skin health and longevity
2. What skin benefits were achieved in human clinical studies testing those foods and supplements
3. What longevity benefits were achieved in human clinical studies testing those foods and supplements
4. Which foods and supplements are still being researched in relation to longevity


bendbeauty.com

T 844.714.7253 Halifax, NS Canada F 902.405.4955

connect@bendbeauty.com

bendbeauty @bendbeauty bend beauty

# Glossary of Terms

**Apoptosis**
A form of programmed cell death that occurs under normal physiological as well as pathological/disease conditions and involves specific changes in shape and biochemical features.

**Epigenetic**
Nongenetic influences on gene expression

**Homeostasis**
The constant state of steady internal, physical, and chemical conditions maintained within living organisms that enables optimal functioning and includes many metabolic variables being kept within limits.

**Mitochondria**
Known as the powerplants within cells, are organelles/"organs" with cells, that create energy from nutrients through a process called cellular respiration.

**Proteostasis**
The process that regulates creation and maintenance of proteins within the cell to maintain their health and that of the organism itself.

**Senescence**
When a cell ages and permanently stops dividing but does not die. During this phase, the cell is essentially in 'suspended animation' because it is resistant to growth-promoting stimuli, typically in response to DNA damage.

# List of Abbreviations

**COPD** = Chronic obstructive pulmonary disorder

**CVD** = Cardiovascular disease

**DNA** = Deoxyribonucleic acid

**NAFLD** = Non-alcoholic fatty liver disease

**PCBs** = Polychlorinated biphenyls

**ROS** = Reactive oxygen species

**UV** = Ultraviolet radiation

# References


1. **Zhou SS, Li D, Zhou YM, Cao JM.** The skin function: a factor of anti-metabolic syndrome. Diabetol Metab Syndr. 2012 Apr 26;4(1):15. doi: 10.1186/1758-5996-4-15. PMID: 22537765; PMCID: PMC3567429. Accessed online on November 9, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3567429/

2. **Davalli P, Mitic T, Caporali A, Lauriola A, D'Arca D.** ROS, Cell Senescence, and Novel Molecular Mechanisms in Aging and Age-Related Diseases. Oxid Med Cell Longev. 2016;2016:3565127. doi: 10.1155/2016/3565127. Epub 2016 May 10. PMID: 27247702; PMCID: PMC4877482. Accessed online on November 11, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4877482/

3. **Moldogazieva NT, Mokhosoev IM, Mel'nikova TI, Porozov YB, Terentiev AA.** Oxidative Stress and Advanced Lipoxidation and Glycation End Products (ALEs and AGEs) in Aging and Age-Related Diseases. Oxid Med Cell Longev. 2019 Aug 14;2019:3085756. doi: 10.1155/2019/3085756. PMID: 31485289; PMCID: PMC6710759. Accessed online on November 11, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6710759/

4. **Giorgi C, Marchi S, Simoes ICM, Ren Z, Morciano G, Perrone M, et al.** Mitochondria and Reactive Oxygen Species in Aging and Age-Related Diseases. Int Rev Cell Mol Biol. 2018;340:209-344. doi: 10.1016/bs.ircmb.2018.05.006. Epub 2018 Jun 22. PMID: 30072092. Accessed online on December 1, 2020 at https://pubmed.ncbi.nlm.nih.gov/30072092/

5. **Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Bonaduce D, Abete P.** Oxidative stress, aging, and diseases. Clin Interv Aging. 2018 Apr 26;13:757-772. doi: 10.2147/CIA.S158513. PMID: 29731617; PMCID: PMC5927356.Accessed online on November 10, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5927356/

6. **Simpkin S.** Cutaneous adverse effects of alcohol. DermNet NZ. 2011. Accessed online on December 5, 2020 at https://dermnetnz.org/topics/cutaneous-adverse-effects-of-alcohol/

7. **Hazin R, Abu-Rajab Tamimi TI, Abuzetun JY, Zein NN.** Recognizing and treating cutaneous signs of liver disease. Cleve Clin J Med. 2009 Oct;76(10):599-606. Accessed online on November 28, 2020 at https://mdedge-files-live.s3.us-east-2.amazonaws.com/files/s3fs-public/issues/articles/media_f0bc644_599.pdf

8. **Majewski S, Pietrzak A, Tworek D, Szewczyk K, Kumor-Kisielewska A, Kurmanowska Z, Górski P, Zalewska-Janowska A, Piotrowski WJ.** Skin condition and its relationship to systemic inflammation in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2017 Aug 11;12:2407-2415. doi: 10.2147/COPD.S141805. PMID: 28860735; PMCID: PMC5565242. Accessed online on November 17, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5565242/

9. **Salem I, Ramser A, Isham N, Ghannoum MA.** The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. Front Microbiol. 2018 Jul 10;9:1459. doi: 10.3389/fmicb.2018.01459. eCollection 2018. Accessed online on March 18, 2019 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6048199/

10. **Saarialho-Kere U.** The gut-skin axis. J Pediatr Gastroenterol Nutr. 2004 Jun;39 Suppl 3:S734-5.

11. **HEART DISEASE 2020: 12 Warning signs that appear on your skin.** American Academy of Dermatology. Accessed online on November 16, 2020 at https://www.aad.org/media/news-releases/skin-can-show-first-signs-of-some-internal-diseases

12. **Gunn DA, de Craen AJ, Dick JL, Tomlin CC, van Heemst D, Catt SD, Griffiths T, Ogden S, Maier AB, Murray PG, Griffiths CE, Slagboom PE, Westendorp RG.** Facial appearance reflects human familial longevity and CVD risk in healthy individuals. J Gerontol A Biol Sci Med Sci. 2013 Feb;68(2):145-52. doi: 10.1093/gerona/gls154. Epub 2012 Aug 9. PMID: 22879455. Accessed online on November 15, 2020 at https://academic.oup.com/biomedgerontology/article/68/2/145/544529

13. **Lee SY, Lee E, Park YM, Hong SJ.** Microbiome in the Gut-Skin Axis in Atopic Dermatitis. Allergy Asthma Immunol Res. 2018 Jul;10(4):354-362. doi: 10.4168/aair.2018.10.4.354. Accessed online on March 18, 2019 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6021588/

14. **Ercolini D, Fogliano V.** Food Design To Feed the Human Gut Microbiota. J Agric Food Chem. 2018 Apr 18;66(15):3754-3758. doi: 10.1021/acs.jafc.8b00456. Epub 2018 Apr 5. Accessed online on March 18, 2019 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5951603/

15. **Thomas CL, Fernández-Peñas P.** The microbiome and atopic eczema: More than skin deep. Australas J Dermatol. 2017 Feb;58(1):18-24. doi: 10.1111/ajd.12435. Epub 2016 Jan 28. Accessed online on March 18, 2019 at https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajd.12435

16. **O'Neill CA, Monteleone G, McLaughlin JT, Paus R.** The gut-skin axis in health and disease: A paradigm with therapeutic implications. Bioessays. 2016 Nov;38(11):1167-1176. doi: 10.1002/bies.201600008. Epub 2016 Aug 24. PMID: 27554239. Accessed online on December 1, 2020 at https://pubmed.ncbi.nlm.nih.gov/27554239/

17. **Markowiak P, Śliżewska K.** Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. Nutrients. 2017 Sep 15;9(9). pii: E1021. doi: 10.3390/nu9091021. Accessed online on December 1, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5622781/

18. **Furman D, Campisi J, Verdin E, et al.** Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822-1832. doi:10.1038/s41591-019-0675-0. Accessed online on November 29, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147972/

19. **Powers CE, McShane DB, Gilligan PH, Burkhart CN, Morrell DS.** Microbiome and pediatric atopic dermatitis. J Dermatol. 2015 Dec;42(12):1137-42. doi: 10.1111/1346-8138.13072. Epub 2015 Sep 21. PMID: 26388516. Accessed online on December 1, 2020 at https://pubmed.ncbi.nlm.nih.gov/26388516/

20. **Clark AK, Haas KN, Sivamani RK.** Edible Plants and Their Influence on the Gut Microbiome and Acne. Int J Mol Sci. 2017 May 17;18(5). pii: E1070. doi: 10.3390/ijms18051070. Accessed online on March 18, 2019 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5454980/

21. **Simpson T, Deleuil S, Echeverria N, Komanduri M, Macpherson H, Suo C, Gondalia S, Fard MT, Pipingas A, Scholey A, Stough C.** The Australian Research Council Longevity Intervention (ARCLI) study protocol (ANZCTR12611000487910) addendum: neuroimaging and gut microbiota protocol. Nutr J. 2019 Jan 5;18(1):1. doi: 10.1186/s12937-018-0428-9. PMID: 30611275; PMCID: PMC6321680. Accessed online on December 10, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6321680/

22. **Kalra A, Tuma F.** Physiology, Liver. [Updated 2018 Dec 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019. Accessed online on October 16, 2019 from: https://www.ncbi.nlm.nih.gov/books/NBK535438/

23. **WebMD What does the liver do?** Accessed online on November 28, 2020 at https://10faq.com/health/what-does-the-liver-do/?utm_source=6953445991&utm_campaign=11322597284&utm_medium=113734710409&utm_content=113734710409&utm_term=what%20does%20the%20liver%20do&gclid=Cj0KCQiAh4j-BRCsARIsAGeV12A9kHl26_cUTWmkocA6o0UZhRCIAngruHAYcSh36PpknnvxQ4K0Hj4aAhg7EALw_wcB

24. **Purkins L, Love ER, Eve MD, et al.** The influence of diet upon liver function tests and serum lipids in healthy male volunteers resident in a Phase I unit. British Journal of Clinical Pharmacology. 2004;57(2):199-208. doi:10.1046/j.1365-2125.2003.01969.x. Accessed online on November 28, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884438/

25. **Cave M, Appana S, Patel M, Falkner KC, McClain CJ, Brock G.** Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: NHANES 2003-2004. Environ Health Perspect. 2010 Dec;118(12):1735-42. doi: 10.1289/ehp.1002720. Accessed online on November 28, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3002193/

26. **Hirashima R, Itoh T, Tukey RH, Fujiwara R.** Prediction of drug-induced liver injury using keratinocytes. J Appl Toxicol. 2017 Jul;37(7):863-872. Accessed online on November 28, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5500258/

27. **Nobili V.** Liver-skin axis: a new view or viewed already? Br J Dermatol. 2018 Jul;179(1):6. doi: 10.1111/bjd.16696. PMID: 30156274. Accessed online on November 28, 2020 at https://pubmed.ncbi.nlm.nih.gov/30156274/

28. **Caccavale S, Bove D, Bove RM, LA Montagna M.** Skin and brain: itch and psychiatric disorders. G Ital Dermatol Venereol. 2016 Oct;151(5):525-9. Epub 2015 Apr 9. Accessed online on June 14, 2019 at https://www.minervamedica.it/en/journals/dermatologia-venereologia/article.php?cod=R23Y2016N05A0525

29. **Reich A, Mędrek K, Szepietowski JC.** Interplay of Itch and Psyche in Psoriasis: An Update. Acta Derm Venereol. 2016 Aug 23;96(217):55-7. doi: 10.2340/00015555-2374. Accessed online on June 14, 2019 at https://www.medicaljournals.se/acta/content/html/10.2340/00015555-2374

30. **Hall H.** Psychodermatology? Science-Based Medicine – Exploring issues and controversies in the relationship between science and medicine. 2018-04-17. Accessed online on July 3, 2020 at https://sciencebasedmedicine.org/psychodermatology/

31. **Koo J, Lebwohl A.** Psycho dermatology: the mind and skin connection. Am Fam Physician. 2001;64(11):1873-1878. Accessed online on July 2, 2020 at https://www.aafp.org/afp/2001/1201/p1873.html

32. **Arck P, Handjiski B, Hagen E, Pincus M, Bruenahl C, Bienenstock J, Paus R.** Is there a 'gut–brain–skin axis'? Experimental Dermatology. 2010;19(5):401-405. Accessed online on June 14, 2019 at https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0625.2009.01060.x.

33. **Suh MG, Hong YH, Jung EY, Suh HJ.** Inhibitory Effect of Galactooligosaccharide on Skin Pigmentation. Prev Nutr Food Sci. 2019;24(3):321-326. doi:10.3746/pnf.2019.24.3.321. Accessed online on March 18, 2019 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6779081/

34. **Boccardi M, Boccardi V.** Psychological Wellbeing and Healthy Aging: Focus on Telomeres. Geriatrics (Basel). 2019 Feb 23;4(1):25. doi: 10.3390/geriatrics4010025. PMID: 31023993; PMCID: PMC6473912. Accessed online on December 5, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6473912/pdf/geriatrics-04-00025.pdf

35. **Feder A, Fred-Torres S, Southwick SM, Charney DS.** The Biology of Human Resilience: Opportunities for Enhancing Resilience Across the Life Span. Biol Psychiatry. 2019 Sep 15;86(6):443-453. doi: 10.1016/j.biopsych.2019.07.012. Epub 2019 Jul 24. PMID: 31466561. Accessed online on December 5, 2020 at https://pubmed.ncbi.nlm.nih.gov/31466561/

36. **Moskalev AA, Aliper AM, Smit-McBride Z, Buzdin A, Zhavoronkov A.** Genetics and epigenetics of aging and longevity. Cell Cycle. 2014;13(7):1063-77. doi: 10.4161/cc.28433. Epub 2014 Mar 6. PMID: 24603410; PMCID: PMC4013158. Accessed online on November 18, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4013158/

37. **Filippopoulou K, Papaevgeniou N, Lefaki M, Paraskevopoulou A, Biedermann D, Křen V, Chondrogianni N.** 2,3-Dehydrosilybin A/B as a pro-longevity and anti-aggregation compound. Free Radic Biol Med. 2017 Feb;103:256-267. doi: 10.1016/j.freeradbiomed.2016.12.042. Epub 2016 Dec 28. PMID: 28039083. Accessed online on November 30, 2020 at https://pubmed.ncbi.nlm.nih.gov/28039083/

38. **Ren J, Zhang Y.** Genetics and Epigenetics in Aging and Longevity: Myths and Truths. Biochim Biophys Acta Mol Basis Dis. 2019 Jul 1;1865(7):1715-1717. doi: 10.1016/j.bbadis.2019.02.005. Epub 2019 Feb 21. PMID: 30799263. Accessed online on November 18, 2020 at https://reader.elsevier.com/reader/sd/pii/S0925443919300572?token=A2194CD198D503E9BC0F4499B45DAF0459CF57DD0F4E2831EE9C4DD8C3643B334F89C86DE7467B5DF3C63D2530C09192

39. **Das SK, Balasubramanian P, Weerasekara YK.** Nutrition modulation of human aging: The calorie restriction paradigm. Mol Cell Endocrinol. 2017 Nov 5;455:148-157. doi: 10.1016/j.mce.2017.04.011. Epub 2017 Apr 12. PMID: 28412520; PMCID: PMC7153268. Accessed online on November 24, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7153268/

40. **Wysocki K, Seibert D.** Genomics of aging: Genes, adducts, and telomeres. J Am Assoc Nurse Pract. 2020 Jun;32(6):419-422. Accessed online on December 7, 2020 at https://pubmed.ncbi.nlm.nih.gov/32511191/

41. **Bousquet J, Cristol J-P, Czarlewski W, Anto JM, Martineau A, Haahtela T et al.** Nrf2-interacting nutrients and COVID-19: time for research to develop adaptation strategies. Clin Transl Allergy. 2020; 10: 58. Accessed online on December 17, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7711617/

42. **Zhang J.** Autophagy and mitophagy in cellular damage control. Redox Biology. 2013;1(1): 19-23. Accessed online on December 7, 2020 at https://www.sciencedirect.com/science/article/pii/S2212231712000109#:~:text=1.,proteins%2C%20lipids%2C%20and%20organelles.&text=Degradation%20of%20mitochondria%20through%20the%20macroautophagy%20pathway%20is%20also%20termed%20mitophagy

43. **Fu M, Zhang X, Zhang X, Yang L, Luo S, Liu H.** Autophagy Plays a Role in the Prolongation of the Life Span of Caenorhabditis elegans by Astaxanthin. Rejuvenation Res. 2020 Nov 30. doi: 10.1089/rej.2020.2355. Epub ahead of print. PMID: 33115330. Accessed online on December 8, 2020 at https://pubmed.ncbi.nlm.nih.gov/33115330/

44. **Yang L, Licastro D, Cava E, Veronese N, Spelta F, Rizza W, Bertozzi B, Villareal DT, Hotamisligil GS, Holloszy JO, Fontana L.** Long-Term Calorie Restriction Enhances Cellular Quality-Control Processes in Human Skeletal Muscle. Cell Rep. 2016a Jan 26;14(3):422-428. doi: 10.1016/j.celrep.2015.12.042. Epub 2016 Jan 7. PMID: 26774472. Accessed online on December 7, 2020 at https://pubmed.ncbi.nlm.nih.gov/26774472/

45. **Djajadikerta A, Keshri S, Pavel M, Prestil R, Ryan L, Rubinsztein DC.** Autophagy Induction as a Therapeutic Strategy for Neurodegenerative Diseases. J Mol Biol. 2020 Apr 3;432(8):2799-2821. doi: 10.1016/j.jmb.2019.12.035. Epub 2019 Dec 27. PMID: 31887286.Accessed online on December 7, 2020 at https://pubmed.ncbi.nlm.nih.gov/31887286/

46. **Tsujimoto, Y.,** Shimizu, S. Another way to die: autophagic programmed cell death. Cell Death Differ 12, 1528–1534 (2005). https://doi.org/10.1038/sj.cdd.4401777 Accessed online on December 7, 2020 https://www.nature.com/articles/4401777#citeas

47. **Cuervo AM, Bergamini E, Brunk UT, Dröge W, Ffrench M, Terman A.** Autophagy and aging: the importance of maintaining "clean" cells. Autophagy. 2005 Oct-Dec;1(3):131-40. doi: 10.4161/auto.1.3.2017. Epub 2005 Oct 13. PMID: 16874025. Accessed online on December 7, 2020 at https://pubmed.ncbi.nlm.nih.gov/16874025/

48. **Varisli L, Cen O, Vlahopoulos S.** Dissecting pharmacological effects of chloroquine in cancer treatment: interference with inflammatory signaling pathways. Immunology. 2020 Mar;159(3):257-278. doi: 10.1111/imm.13160. Epub 2019 Dec 22. PMID: 31782148; PMCID: PMC7011648. Accessed online on December 7, 2020 at https://pubmed.ncbi.nlm.nih.gov/31782148/

49. **Giunta S.** Is inflammaging an auto[innate]immunity subclinical syndrome?. Immun Ageing. 2006;3:12. Published 2006 Dec 16. doi:10.1186/1742-4933-3-12 Accessed online on December 6, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1716179/

50. **Ferrucci L, Fabbri E.** Inflammageing: chronic inflammation in ageing, CVD, and frailty. Nat Rev Cardiol. 2018;15(9):505-522. doi:10.1038/s41569-018-0064-2. Accessed online on December 6, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6146930/

51. **Franceschi, C.,** Garagnani, P., Parini, P. et al. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. Nat Rev Endocrinol 2018;14:576–590. https://doi.org/10.1038/s41574-018-0059-4. Accessed online on December 6, 2020 at https://www.nature.com/articles/s41574-018-0059-4

52. **Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R.** Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A. 2003;100(15):9090-9095. doi:10.1073/pnas.1531903100. Accessed online on December 6, 2020 at https://pubmed.ncbi.nlm.nih.gov/12840146/

53. **Franceschi C, Garagnani P, Vitale G, Capri M, Salvioli S.** Inflammaging and 'Garb-aging' Trends in Endochronology and metabolism. 2017; 28(3): 199-212. Accessed online on December 6, 2020 a thttps://www.cell.com/trends/endocrinology-metabolism/fulltext/S1043-2760(16)30125-4?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1043276016301254%3Fshowall%3Dtrue

54. **Montecino-Rodriguez E, Berent-Maoz B, Dorshkind K.** Causes, consequences, and reversal of immune system aging. J Clin Invest. 2013 Mar;123(3):958-65. doi: 10.1172/JCI64096. Epub 2013 Mar 1. PMID: 23454758; PMCID: PMC3582124. Accessed online on December 6, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3582124/

55. **Panda A, Arjona A, Sapey E, et al.** Human innate immunosenescence: causes and consequences for immunity in old age. Trends Immunol. 2009;30(7):325-333. doi:10.1016/j.it.2009.05.004 Accessed online on December 6, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4067971/

56. **Zamboni M, Nori N, Brunelli A, Zoico E.** How does adipose tissue contribute to inflammageing? Exp Gerontol. 2020 Nov 27:111162. doi: 10.1016/j.exger.2020.111162. Epub ahead of print. PMID: 33253807.Accessed online on December 6, 2020 at Accessed online on December 6, 2020 at https://pubmed.ncbi.nlm.nih.gov/33253807/

57. **Zhang J, Rane G, Dai X, Shanmugam MK, Arfuso F, Samy RP, Lai MK, Kappei D, Kumar AP, Sethi G.** Ageing and the telomere connection: An intimate relationship with inflammation. Ageing Res Rev. 2016;25:55–69. Accessed online on Oct 9, 2020 at https://pubmed.ncbi.nlm.nih.gov/26616852/

58. **Arsenis NC, You T, Ogawa EF, Tinsley GM, Zuo L.** Physical activity and telomere length: Impact of aging and potential mechanisms of action. Oncotarget. 2017;8(27):45008-45019. doi:10.18632/oncotarget.16726. Accessed online on Oct 9, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5546536/

59. **Orioli D, Dellambra E.** Epigenetic Regulation of Skin Cells in Natural Aging and Premature Aging Diseases. Cells. 2018 Dec 12;7(12):268. doi: 10.3390/cells7120268. PMID: 30545089; PMCID: PMC6315602. Accessed online on November 18, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6315602/

60. **Victorelli S, Passos JF.** Telomeres and Cell Senescence - Size Matters Not. EBioMedicine. 2017 Jul;21:14-20. doi: 10.1016/j.ebiom.2017.03.027. Epub 2017 Mar 21. PMID: 28347656; PMCID: PMC5514392. Accessed online on December 7, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5514392/

61. **Solway J, McBride M, Haq F, Abdul W, Miller R.** Diet and Dermatology: The Role of a Whole-food, Plant-based Diet in Preventing and Reversing Skin Aging-A Review. J Clin Aesthet Dermatol. 2020 May;13(5):38-43. Epub 2020 May 1. PMID: 32802255; PMCID: PMC7380694. Accessed online on November 2, 2020 at https://pubmed.ncbi.nlm.nih.gov/32802255/

62. **Vidacek NŠ, Nanic L, Ravlic S, Sopta M, Geric M, Gajski G, Garaj-Vrhovac V, Rubelj I.** Telomeres, Nutrition, and Longevity: Can We Really Navigate Our Aging? J Gerontol A Biol Sci Med Sci. 2017 Dec 12;73(1):39-47. doi: 10.1093/gerona/glx082. PMID: 28510637. Accessed online on December 7, 2020 at https://pubmed.ncbi.nlm.nih.gov/28510637/

63. **Wissler Gerdes EO, Zhu Y, Weigand BM, et al.** Cellular senescence in aging and age-related diseases: Implications for neurodegenerative diseases. Int Rev Neurobiol. 2020;155:203-234. doi:10.1016/bs.irn.2020.03.019 Accessed online on December 10, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7656525/

64. **Burton DG, Krizhanovsky V.** Physiological and pathological consequences of cellular senescence. Cell Mol Life Sci. 2014;71(22):4373-4386. doi:10.1007/s00018-014-1691-3. Accessed online on December 6, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4207941/

65. **Antonangeli F, Zingoni A, Soriani A, Santoni A.** Senescent cells: Living or dying is a matter of NK cells. Journal of Leucocyte Biology. 2019;10(6):1275-1283. Accessed online on December 6, 2020 at https://jlb.onlinelibrary.wiley.com/doi/abs/10.1002/JLB.MR0718-299R

66. **Smith J A, Daniel R.** Stem Cells and Aging: A Chicken-Or-Egg Issue?. Aging and Disease. 2012;3(3): 260–268.

67. **Ren R, Ocampo A, Liu GH, Izpisua Belmonte JC.** Regulation of Stem Cell Aging by Metabolism and Epigenetics. Cell Metab. 2017 Sep 5;26(3):460-474. doi: 10.1016/j.cmet.2017.07.019. Epub 2017 Aug 17. PMID: 28826795. Accessed online on December 7, 2020 at https://pubmed.ncbi.nlm.nih.gov/28826795/

68. **Trüeb RM, Henry JP, Davis MG, Schwartz JR.** Scalp Condition Impacts Hair Growth and Retention via Oxidative Stress. Int J Trichology. 2018 Nov-Dec;10(6):262-270. doi: 10.4103/ijt.ijt_57_18. Accessed online on July 16, 2019 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6369642/

69. **Matsumura H, Mohri Y, Binh NT, Morinaga H, Fukuda M, Ito M, Kurata S, Hoeijmakers J, Nishimura EK.** Hair follicle aging is driven by transepidermal elimination of stem cells via COL17A1 proteolysis. Science. 2016 Feb 5;351(6273):aad4395. doi: 10.1126/science.aad4395. Epub 2016 Feb 4. PMID: 26912707. Accessed online on December 7, 2020 at https://pubmed.ncbi.nlm.nih.gov/26912707/

70. **Bektas A, Schurman SH, Sen R, Ferrucci L.** Aging, inflammation and the environment. Exp Gerontol. 2018 May;105:10-18. doi: 10.1016/j.exger.2017.12.015. Epub 2017 Dec 21. PMID: 29275161; PMCID: PMC5909704. Accessed online on Oct 9, 2020 at https://pubmed.ncbi.nlm.nih.gov/29275161

This book is not intended to provide medical advice or to take the place of medical advice and treatment from your personal physician. Readers are advised to consult their doctors or qualified health professionals regarding specific health questions. Neither the publisher nor the author takes responsibility for the possible health consequences of any person reading or following the information in this book. All readers, especially those taking prescription or over-the-counter medications, should consult their physicians before beginning any nutrition or supplement program.

**† These statements have not been evaluated by the Food and Drug Administration. This book is not intended to diagnose, treat, cure or prevent any disease.**