Healthy Living Into Your Second Century

Bringing Youthfulness To Longevity

Cellular and Connective Tissue Renewal

Dietary Supplement

4th generation product

Supplement Facts

Serving Size 2 Capsules
Servings Per Container 30

Amount Per Serving		% Daily Value
Vitamin D3 (as cholecalciferol)	1000 IU	250%
Longevinex® patent pending Proprietary Blend	365 mg	†

Extracts of Giant Knotweed *(Polygonum cuspidatum)* providing 100 mg of micronized, microencapsulated trans resveratrol per two capsules, grape seed extract, quercetin, ferulic acid, cocoa extract (theobromine), Biolut® lutein, green tea extract, rice bran phytate (IP6), and pure hyaluronan.

† Daily value not established.

Other Ingredients: modified vegetable starch and dextrin matrix, plant cellulose, titanium dioxide, candelilla wax, silicon dioxide, dicalcium phosphate anhydrous.

NEW!

Proven 9 Times More Effective Than Plain Resveratrol**

First to combine natural molecules from Cocoa and Red Wine

- Designed to renew aged cells and connective tissue; promotes youthful appearance (hair, skin); cellular function.*
- Provides mineral-chelating (key-lay-ting) molecules as naturally found in red wine grapes, cocoa and bran; designed to reverse calcification and rusting of tissues.*
- Proven to activate 9-times more longevity genes than plain resveratrol (mouse study).*
- Resveratrol is stabilized by microencapsulation for prolonged shelf life.*
- Micronized resveratrol to improve absorption.*
- Ingredients work synergistically to accentuate biological action.*

Suggested Use: As a dietary supplement, take 2 capsules per day, with a meal. Not intended for children, pregnant women or anemic individuals.

***Experimental Gerontology Volume 43: 859, 2008*

Providing 100 milligrams trans resveratrol per capsule
Suggested daily serving size: 1-2 capsules daily

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

Longevity & Youthfulness

ADVANTAGE+™

LONGEVINEX®

*A World's First: Promotes Healthy Cells and Connective Tissue s**
Provides Red Wine Antioxidants, Resveratrol and Hyaluronan

Longevinex' first-generation dietary supplement was the first to stabilize trans resveratrol. Now we are proud to introduce Longevinex Advantage™, the ultimate dietary supplement for consumers searching for youthful renewal and longevity. It is the first dietary supplement to address both cellular and connective tissue aging.

Americans have achieved unprecedented longevity. Twenty-five percent of Americans will live beyond the age of 92. Many Americans have begun to take red wine resveratrol pills like Longevinex®, in hopes of extending their lives another 20 to 30 years. Biologists now say the 120-year lifespan may soon become the norm.

But superlongevity has its price --- the loss of youthful appearance and activity levels. Hair withers, skin wrinkles, joints creak. The reason? As the human body ages it begins to lose a key water-holding molecule called hyaluronan that serves as a space filler, cushioning and hydrating agent in the skin, eyes, hair and joints. Longevinex Advantage™ provides a unique source of pure oral hyaluronan which stimulates cells in the body to produce more hyaluronan. The goal is to restore aging tissues to youthful levels of hyaluronan.

Resveratrol is a natural molecule that stimulates DNA repair and longevity of cells via gene activation as well as other molecular pathways. The combination of resveratrol and hyaluronic acid is the subject of an applied-for patent.

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How To Live 100 Years Without Growing Old

Americans Are Living Longer, And Starting To Take Anti-Aging Pills. But How Old Will You Appear When You Are 82, or 102, or 122?

Americans can expect to live longer than their forefathers. But there is one curse of longevity that the mirror reveals --- we all look old. The graying hair, the raspy voice, the continual need for reading glasses, are unpleasant reminders of progressive aging. Fortunately, there may be new ways to retain a youthful appearance, or even reverse visible signs of aging. Such a development comes none too soon for the population of American Baby Boomers that are now entering their retirement years.

Have you ever heard anyone say, *"Why you look so young for your age."* Why do some people look older than their peers?

Obviously, **your calendar age and your biological age may differ**. If you follow the theory of aging proposed by Longevinex®, that cellular aging doesn't begin till full growth is achieved (~ age 18 years – see UNIFIED THEORY OF AGING at the Longevinex® website), then you will recognize aging is not the same as the number of birthdays you have accumulated.

Furthermore, it becomes clear that the outer organs of the body, **the skin, hair and eyes, may age faster than internal organs due to chronic exposure to solar ultraviolet radiation**.

The visible signs of aging, facial wrinkles, graying and thinning of hair, and hair loss, and changes in vision (need for reading glasses) predominate in creating the perceived appearance of aging.

A study of facial aging conducted among twins reveals that 40% of the variation in their perceived age was due to non-genetic factors, namely sun exposure and smoking. Both of these environmental factors degrade connective tissue (collagen).[1] Frequent consumption of alcoholic beverages has also been shown to correlate with an older appearance.[2]

More interest in retaining youthfulness than longevity

In this 21st Century, Americans are living longer than once imagined. Americans are living into their 8th and 9th decades of life and some experts say that middle-aged Americans are going to live beyond 100 years with greater regularity. Imagine reaching the age of 70 and you still have another 30-50 years ahead of you.

So there is a growing interest in retaining a youthful appearance as aging progresses. In fact, **many Americans are more interested in retaining a youthful appearance than they are in living longer.** Just look at the number of people who use hair dye, skin creams, wear contact lenses, and elect to undergo plastic surgery, in an effort to retain a youthful appearance. Compare that to the few who practice calorie restriction or take an anti-aging pill to prolong their lifespan.

A relatively small but growing number of Americans are venturing on their own, ahead of unfolding research, to consume what they believe to be an anti-aging pill that will add another 30-50 years of healthy living to their lifespan. The current rage, spawned from the discovery that it may be possible to molecularly mimic the benefits of a limited calorie diet, has created a group of longevity-seekers that want to live far longer than their forefathers.

The Rand Institute has already advised Medicare to budget for such a pill. Many Americans may live 120 years in good health if ongoing research confirms the biological action of resveratrol.

Figure 1 TIME How to live to be 100 (and not regret it) August 30, 2004

A seeming setback in this pursuit occurred when the human equivalent of 360 mg and 1565 mg of resveratrol shortened the lifespan of laboratory mice. Resveratrol by itself may not mimic calorie restriction.

However, it is widely known that the red wine-drinking French have far more centenarians per capita than any other developed country. Professor Roger Corder of the Harvey Research Institute in London, asserts it is the total number and quantity of red wine molecules (resveratrol, quercetin, catechin, ferulic acid, gallic acid, kaempferol) in red wine, about 60 milligrams per 5-ounce glass, that exerts life-prolonging activity. It is widely known that 3-5 glasses of red wine providing about 180-300 mg of red wine molecules, produce health benefits. This is what Longevinex® attempts to provide.

A compelling mouse study shows that Longevinex® activates 9-fold more longevity genes that plain resveratrol or a calorie restricted diet.

The good news is, if pills that mimic calorie restriction live up to their billing, Americans won't have to deprive themselves of food to live longer. But they may have to live with more wrinkles.

Fast forward your picture album to imagine what you are going to look like at age 82, or 102, or 122.

The person who lived the longest in modern times was **Jeanne Calment** of France (February 21, 1875 – August 4, 1997: 122 years). Jeanne drank French wine daily, so resveratrol may have contributed to her longevity. Here is what Jeanne looked like at various ages.

What happened to Jeanne over the years? Why did her skin dry out and become wrinkled? Why did her lips narrow and her hair become thin? Jeanne retained her mental acuity and her motor function. At age 100 she rode a bicycle and recorded a song after her 100th birthday. She had a good sense of humor at age 115. But she physically looked older and older.

An unkind reality is that resveratrol-pill users may live longer but not appear to be any younger. However, there are biological mechanisms that can be altered to help *"longevinarians"* retain a youthful appearance, which is the subject of the remainder of this paper.

Theories of aging: do they address the visible signs of aging?

There are many theories of aging – the free radical/antioxidant theory, the mitochondrial theory, the cellular debris theory (autophagy), the DNA gene mutation theory, the telomere theory (chromosome shortening), among many. **These are all cellular theories of aging**. These theories center around mechanisms and interventions that would help keep the trillions of living cells in the body performing at youthful levels.

Figure 2 Jeanne Calment of France, shown at age 60, 113 and 120 years. Ms. Calment lived longer than any modern human, 122 years.

However, the human body is more than trillions of cells stratified into tissues and organs. **There is also *"goo,"* non-cellular material that links or connects all the cells and serves as a space filler. This is called connective tissue** (also called collagen or *"ground substance."*) Connective tissue is akin to mortar that holds bricks together.

If the *"goo"* is not maintained, humans will appear to be prematurely old.

Within connective tissue is a *key water-gelling molecule called hyaluronan (hyaluronic acid, or HA*). This is the molecule that expands connective tissue and acts as a space filler or scaffolding for the skin, joints, eyes and hair.

HA has the capacity to hold water better than any other natural or synthetic substance. It is the shock absorber or spongy collagen at the end of bones. HA is also concentrated in the synovial lubricating fluid in the joints, in hair follicles and is the gel that fills the eyes. Without adequate HA the skin wrinkles and dries, bone rubs on bone, the voice becomes raspy, blood vessels weaken, the eyes shrink in their sockets and corrective lenses are needed, healing is poor and tissues lose elasticity.

HA produces scarless wound healing, particularly evident during the youthful years and in facial skin where HA is abundant. A man who cuts his face while shaving will not produce a scar. HA is also abundant in fingertips as a cushioning agent for nerves. Therefore, small fingertip cuts usually heal without scarring.

High tissue levels of HA are found during youth. See the photo here of the folds of skin shown on a Sharpei dog and a young baby. The skin folds are filled with HA.

Figure 3 Baby shown with sharpei dog. Skin folds are evidence of abundant hyaluronan. Babies are the picture of youth because of abundant hyaluronan a water-gelling molecule that serves as a space-filler and cushioning agent.

Premature aging

Of particular interest is a premature aging syndrome called **progeria** (Hutchinson-Gilford syndrome)

Figure 4 Progeria child appears prematurely old, but mental function is normal. Cataracts removed from this child required thick eyeglasses. Also note complete loss of hair and eyebrows and lashes.

where signs of aging begin to appear in infancy. (Progeria is coined from the Greek word *"geraios"*, meaning old.) Progeric children will exhibit hair loss, wrinkling of the skin, bone deterioration, premature cataracts and need for reading glasses, but their mental development appears normal. Progeric children also do not have a long lifespan, most succumbing to this rare aging syndrome before the age of 20. **Progeric children excrete up to 17 times more hyaluronan than normal children.** These children are losing HA faster than their bodies can replace it.

Age-related loss of HA

Of great interest is animal research published over a decade ago showing that circulating levels of HA are high during youth, decline with advancing age, and then rise against in old age. The rise in HA levels with age can be explained by the fact more HA is being degraded and excreted in the blood circulation.[3]

The human body has a high turnover rate for HA. About 1000-3000 milligrams is degraded and metabolized in the liver or excreted in the lymph or urine daily, and it is rapidly replaced by production from cells called **fibroblasts**.

HA holds water in the body. About two-thirds of the human body is water (about 40-50 quarts for a 160-pound adult). About 1000 milligrams of HA can hold up to 6 liters (~quart) of water in the body, so excessively rapid loss of HA can result in humans turning from a *"luscious juicy plum, to a shriveled up dehydrated prune."*

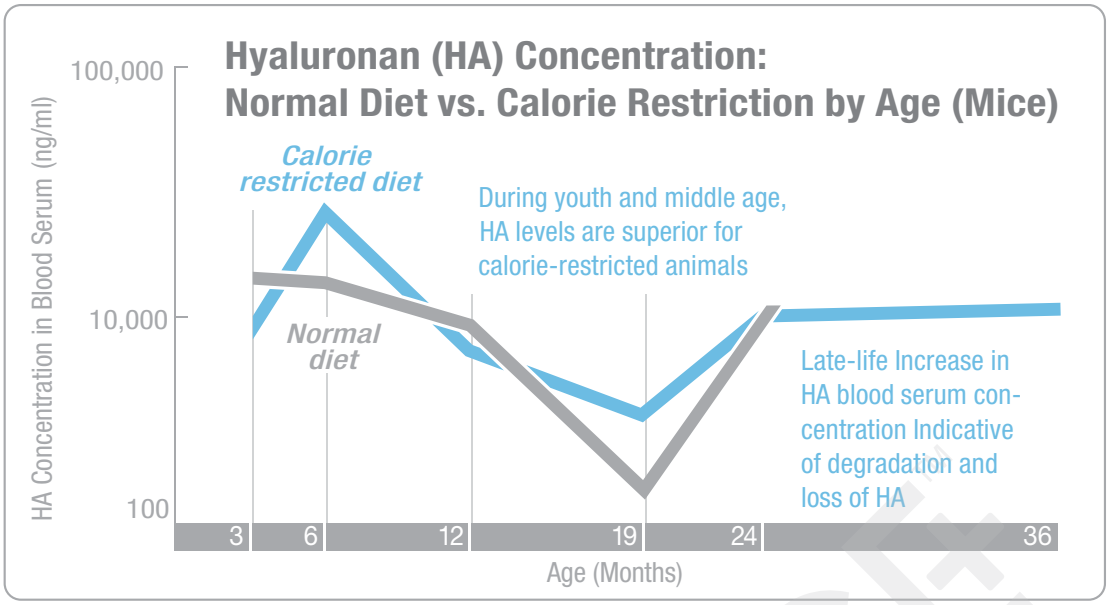
In humans there is marked loss of HA after age 60. However, there are dietary factors that influence the loss of HA.

Researchers have found that a calorie restricted diet helps to maintain more youthful levels of HA. In an experiment conducted with rodents, **a calorie restricted diet reduced the loss of HA age-related loss of HA.** Notice the calorie-resticted animals lived far longer (36-months compared to 24 months.[4]

There is **speculation that a molecular calorie-restriction mimic may produce the same effect**, though further research is needed. It has been shown that, unlike other estrogen-like molecules in plants (genistein in soy), resveratrol does not interrupt sex hormones and activates osteoblast cells that produce bone in a similar manner to estrogen.[5]

Worldwide astonishment: Yuzurihara, Japan

The idea that HA is a youth-promoting molecule moved outside of the laboratory when news reporters focused on a tiny village located about an hour and a half outside of Tokyo, Japan. Here ABC News Prime Time Live sent camera crews to show people who live in Yuzurihara, Japan – people who are 80 and 90 years old but appear to be decades younger. The residents of Yuzuirhara had birth certificates to prove their calendar age. The TV pictures astonished audiences when they were broadcast worldwide in the year 2000.



Reference: Circulating hyaluronan levels in the rodent: effects of age and diet. Am J.Physiol. 268: C952-57, 199 5

Figure 5 Top graph shows middle-age decline in circulating hyaluronan in mice. Bottom graph shows less decline in circulating hyaluronan levels in middle age mice with calorie-restricted diet. Note: calorie-restricted mice lived much longer (24 vs 36 months).

The town doctor, Dr. Komori, who has written extensively on this phenomenon, cites **youthful levels of hyaluronan as the factor involved in the young appearance of these long-lived villagers**. In fact, in regard to longevity, there are 10 times more people living beyond the age of 80 in Yuzurihara than any town in the USA. According to the World Health Organization, the longest-lived people in the world live in Japan and Yuzurihara is heads above 990 Japanese villages and towns surveyed in longevity.

Figure 6 80-year old man in Yuzurihara works daily in his vegetable garden

Here were people living to advanced ages without wrinkles, without the typical age-related diseases and maintaining active lifestyles. Some adults, even life-long smokers who had worked in the outdoors exposed to sunlight all their lives, had virtually no wrinkles. **Health authorities attribute this youthfulness to the unique diet in Yuzurihara that encourages the maintenance of HA.**

Modern medicine adopts HA replacement technology

Modern medicine has not overlooked hyaluronic acid. HA has been used as a lubricant in eye surgery for over a decade. Dermatologists now inject high-molecular weight HA into the skin to reduce wrinkles. Orthopedists inject high-molecular weight HA into knee, shoulder, sacroiliac, intervertebral discs and the temporomandibular joint (jaw) to reduce joint inflammation. The success rate of inject-

Figure 7 80-year old man in Yuzurihara, on motorcycle

able HA in relieving joint problems is about 80 percent, though the effect is transient. HA is now being used in prescription eye drops, in skin preparations and to prevent adhesions following surgery. So the HA revolution is underway.

However, in Japan, oral consumption of HA has become quite popular with over $4 billion of HA dietary supplements and topical formulas being sold. Most Americans have yet to catch on to the rejuvenating properties of HA.

Hormones and visible signs of aging

At the time news reporters surmised that the youthful appearance of these people in Yuzurihara to their consumption of *"sticky vegetables,"* in particular a dish called tamaji that consisted of boiled potatoes. However, a personal trip to Yuzurihara found nothing unusual about the potatoes, but rather the miso paste that was poured on top. Miso is a fermented source of soy and the fermentation concentrates weak estrogen-like molecules found in soy.

By virtue of their production of estrogen, women exhibit smoother skin, thicker hair and more flexible joints than equally-aged males. This is because **estrogen triggers the production of HA in tissues throughout the body.**

The highest levels of HA in the human body are produced during pregnancy when estrogen levels are also at their peak. A pregnant woman has the thickest hair, smoothest skin and most flexible joints. In fact, in preparation for birth, HA levels in the uterine cervix rise dramatically and this tissue undergoes a remarkable transformation from a closed, rigid structure to an elastic, remodeled structure that stretches to allow passage of a baby.[6]

Researchers at the University of St. Andrews have graphically shown that women's facial features appear more full and attractive when their estrogen levels are highest.[7]

Figure 8 Hyaluronan levels are highest when estrogen levels are at their peak during pregnancy. Pregnant women display the smoothest skin and thickest hair.

Figure 9 Men found the woman's face on the left (who had higher estrogen levels) more attractive than the one on the right.

Decline of estrogen = decline in HA

It has been well documented that the onset of menopause and decline in estrogen production in females results in acceleration of skin aging, dryness, wrinkles, and hair loss. Estrogen replacement increases skin thickness and reverses many of the aging changes in the skin.[8, 9,10]

The average wrinkle score for women is reduced modestly with hormone replacement.[11]

In an anthropological study, the Japanese living in Japan have been shown to have thicker hair than North Americans.[12] This may be due to their traditional diet that is abundant in phytoestrogens (plant estrogens) rather than a solely controlled genetic trait.

Estrogen replacement falls out of favor

However, estrogen replacement therapy has fallen out of favor since a major study published in 2002 showed that while it may alleviate subjective symptoms of menopause (hot flashes), it may also slightly increase the risk for breast cancer, heart attacks, strokes and blood clots. Those risks outweighed the drugs' benefits -- a small decrease in hip fractures and a decrease in colorectal cancer.[13]

Other agents that stimulate HA

The drawbacks of estrogen replacement therapy give rise to the question, can phytoestrogens stimulate the production of HA?

A number of agents can stimulate the production of hyaluronan.[14]

Topical application of estrogen to the skin increases the activity of hyaluronic acid synthetase, the enzyme that promotes the production of HA.[15]

Plant estrogens (phytoestrogens)

Weak estrogen-like molecules, concentrated in fermented sources of soy, such as miso and tempeh, help to stimulate synthesis of hyaluronan, thus averting many of the visible signs of aging observed in the eyes, skin, hair and joints. This may be the reason for the unusual youthfulness displayed among residents of Yuzurihara, Japan. **Certainly phytoestrogens are safer than estrogen replacement therapy.**

Of particular interest is the demonstration in two different studies that a soy extract and genistein and daidzein, two soy molecules, can also stimulate the production of hyaluronan when placed in a lab dish with epidermal cells.[16,17]

HA stimulated by glucosamine, chondroitin, hyaluronan

Glucosamine and chondroitin supplements, frequently used for joint health, are precursors of HA. Glucosamine is actually one half of the HA molecule.[18]

In a study of 53 females given an oral glucosamine supplement that included minerals and accompanying antioxidants, a significant reduction in fine lines and wrinkles was observed following a 5-week regimen.[19]

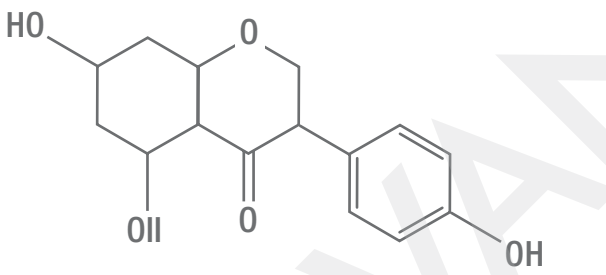
More recently it was discovered that **HA itself stimulates the production of more HA.** A popular injectable HA product, when injected into the skin of humans, was found to prompt tissues to produce more HA.[20] Oral HA supplements produce quicker tissue response and are preferred over glucosamine or chondroitin.

Earlier studies, published in 1987, also confirm that when HA is added to a lab dish with cells taken from the inner-fluid drain of the eye (trabecular meshwork) or to fibroblast cells derived from the synovial fluid of the knee, more HA is produced.[21, 22]

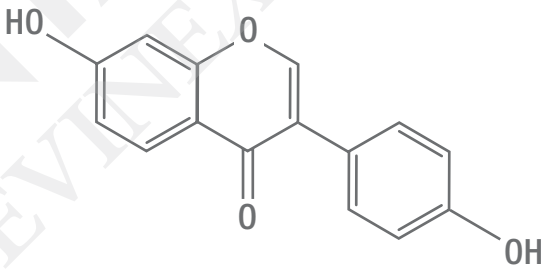
Oral absorption

Many physicians tell their patients that oral hyaluronan cannot be absorbed because it is too large of a molecule. However, studies confirm that oral HA is absorbed in small amounts, apparently enough to stimulate fibroblast cells to produce more HA.[23]

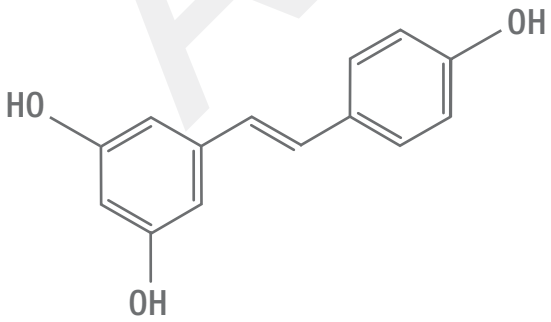
Oral HA supplements have also been shown to be beneficial for joint health in horses.[24]



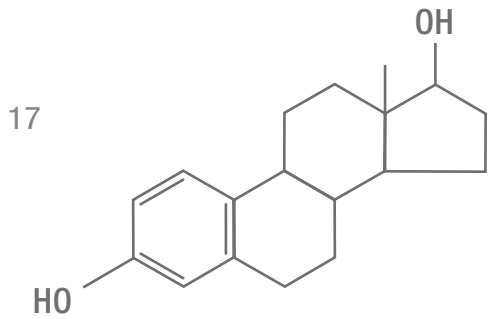
1 **GENISTEIN** (4', 5, 7-trihydroxyisolavone)



2 **DAIDZEIN** (4', 7-dihydroxyisoflavone)



3 **RESVETRATROL**



4 **17β-ESTRADIOL**

Figure 10 Similarity of two estrogen-like soy molecules (genistein, daidzein) with resveratrol and natural estrogen (estradiol)

Stomach acid chops down HA

While hyaluronan is a long strand, high molecular weight molecule consisting of alternating glucosamine and glucuronic acid molecules, oral HA supplements are subject to degradation by stomach acid. Any long-chain HA will be broken down during digestion in order to facilitate absorption. In addition to stomach acid, stomach enzymes, in particular the enzyme hyaluronidase, breaks down HA to smaller fragments.[25]

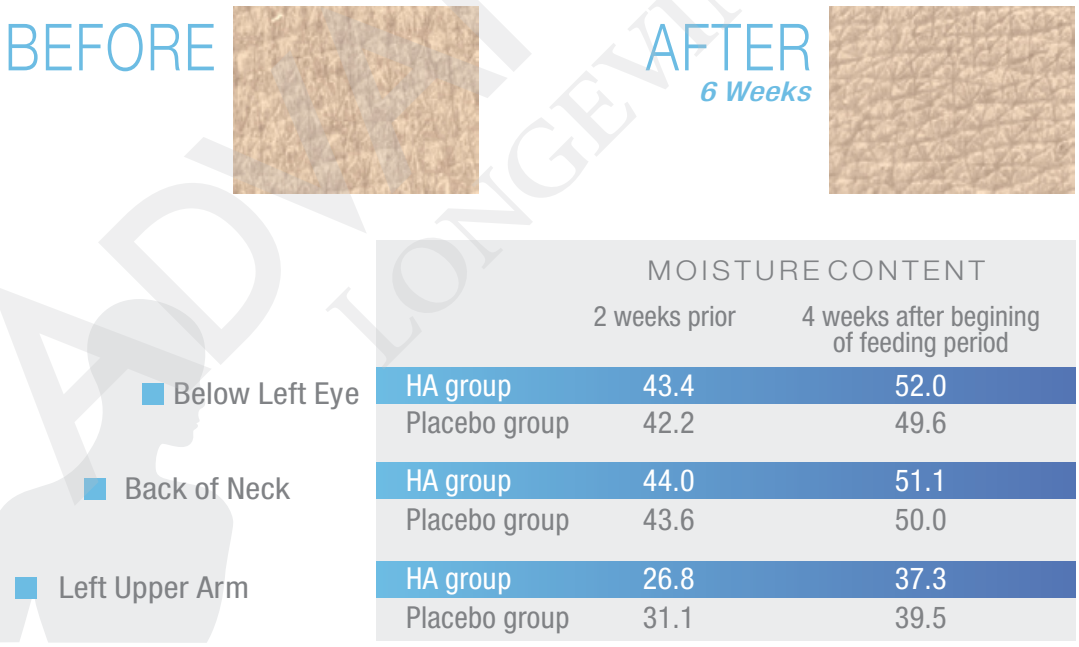
For comparison, chondroitin is a similar type of high molecular weight collagen product sold for the purpose of improving joint health A study of oral chondroitin sulfate in horses shows that chondroitin is not absorbed as an intact molecule, but rather as a shortened molecule.[26]

Safety concerns of phytoestrogens

Undue concern has arisen that plant estrogens like resveratrol may induce hormone-related (breast, uterine) cancer. Studies show there is no evidence that plant estrogens increase the risk for breast cancer.[27] Asian populations that consume large amounts of soy obtain a 17-73% reduction in risk for breast cancer.[28]

A common mistake made by cancer doctors and nurses is their communicated fear that plant estrogens promote cancer growth. The dual nature of phytoestrogens is not considered. Plant estrogens act both as pro-estrogen and anti-estrogens.[29]

Phytoestrogens are very weak, about 1,000th the activity of natural estrogen, with resveratrol exhibiting 1/7,000th the activity of estrogen. Furthermore, while plant estrogens may promote tumor cell growth in lab dishes, they may not in the body. Resveratrol, an estrogen-like molecule, has been shown to exhibit no breast cancer promotional effects.[30]



	MOISTURE CONTENT	
	2 weeks prior	4 weeks after begining of feeding period
HA group	43.4	52.0
Placebo group	42.2	49.6
HA group	44.0	51.1
Placebo group	43.6	50.0
HA group	26.8	37.3
Placebo group	31.1	39.5

Clinical effects of dietary hyaluronic acid on dry, rough skin. Aesthetic Dermatology Vol 12: 100-120, 2002

Figure 11 Changes in Moisture Content of the Skin Among Subjects Given

Human clinical study

A controlled human clinical study of oral hyaluronan is instructive. Among 35 subjects with dry, rough skin, all were given an oral hyaluronan supplement (60 milligrams consumed twice a day, or 120 mg total per day, taken after a meal). Measurements of skin moisture showed that **oral HA acted to increase moisture content and microscopic skin surface analysis showed HA increased skin smoothness and minimized wrinkles.** The clinical improvement in the skin was correlated with an increase in blood serum concentration of HA corresponding to supplementation. Oral hyaluronic acid was deemed safe and did not significantly alter liver enzymes, cholesterol, triglycerides, or electrolyte mineral levels.[31]

These exclusive photos show the rapid improvement in skin smoothness and moisture after a short-course of oral hyaluronan supplementation (Source: QP Corp.)

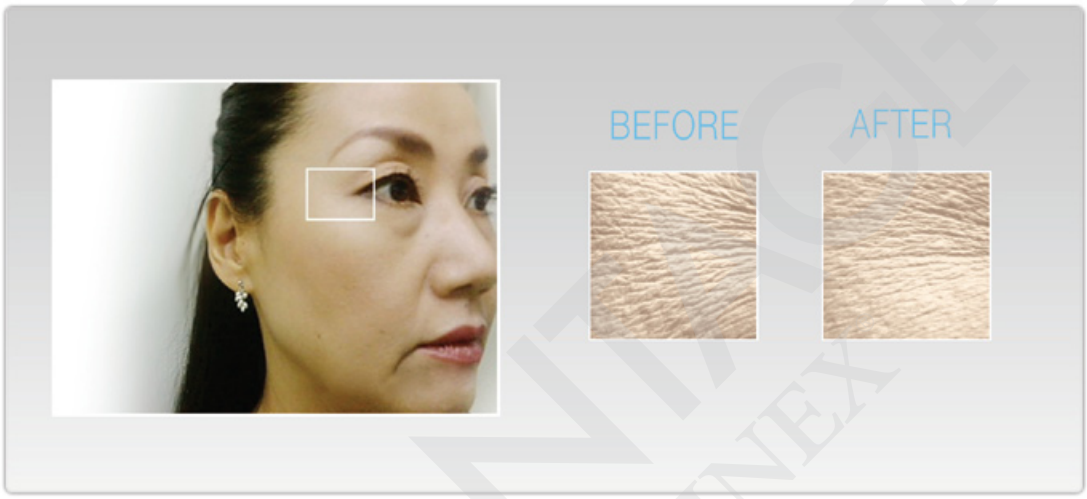


Figure 12 Improvement in skin smoothness and moisture in eye area following 6 weeks of oral hyaluronan supplementation

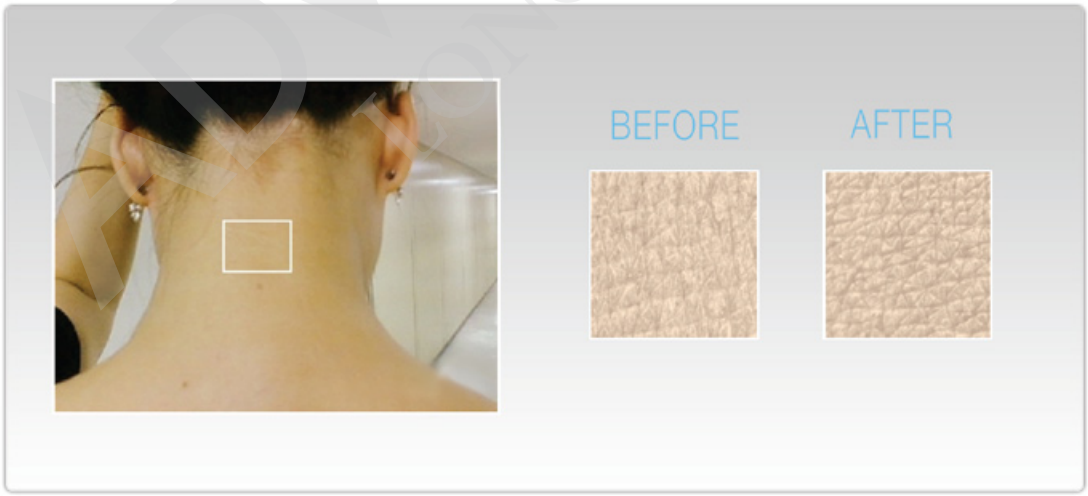


Figure 13 Improvement in skin smoothness and moisture at back of neck 4 weeks after oral hyaluronan supplementation.

Figure 14 Disappearance of fine lines around the eyes after four months of oral hyaluronan supplementation. Photo provided by subject. Photo at left taken in July 2003, photo at right October 2003.

Perceived age and voice

The sound of the human voice can convey age. Many people solely assess perceived age by the youthful or aged sound of another person's voice on the telephone.

Figure 15 Your telephone voice often conveys your perceived age. Hyaluronan levels decline with advancing age and the voice begins to sound raspy, strained or hoarse.

As expected, women have higher levels of HA in their vocal cords compared to men.[32]

The aging voice is characterized as a vocal cord problem resulting in reduced loudness, hoarseness, voice strain and raspiness.[33]

Theoretically, oral hyaluronic acid supplements should also produce a more youthful sounding voice. Aged fibroblast cells in the vocal cords produce less HA. Researchers claim **hyaluronan must be reinstated to more youthful levels to restore vocal cords to a younger state**.[34] Anecdotal reports confirm that HA supplements may be promising in maintaining and restoring a more youthful sounding voice.

Summary

Living longer presents unprecedented challenges. A youthful appearance is treasured by many people as they age. Supplemental hyaluronan, delivered by injection or oral dose, is revolutionizing efforts to heal, rebuild and maintain the form and function of the human body.

The unique combination of resveratrol and hyaluronan addresses the desire of many adults to pursue a long and healthy life with maximum perceived youthfulness.

The additional provision of natural antioxidants (quercetin, rice bran IP6 phytate) and sunscreen agents (ferulic acid) in Longevinex® Advantage™ serve to help maintain youthful levels of HA. The unique combination of resveratrol, hyaluronan and other ingredients is the subject of a US Patent application.

Bill Sardi

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