

This white paper will outline the mechanism of hyaluronic acid promoting joint health and skin beauty, as well as the clinical data of HAPLEX® Plus.



How Hyaluronic Acid could promote joint health and skin beauty?

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1. Introduction

1.1 The joint health supplements market driven by an aging and sports population

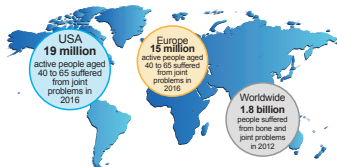
Nowadays people around the world are living longer and heavier and people are paying more and more attention on the joint health especially in US and Europe. It is estimated that the over-60 age group will jump from 800 million to 2 billion people by 2050, thus comprising 22% of the world population.

The aging demographics is not the only consumer group that shows a growing interest for bone and joint care supplements. The athlete and fitness groups demonstrate a surging demand for bone and joint care supplements for various purposes: improve performance, release pain and inflammation, enhance tissue repair and recovery time^[1].

The bone and joint care supplements market had reached 9 billion US Dollars by 2017. Joint health consumers can be mainly divided into three

groups: Baby Boomers who hope to continue an active lifestyle, Overweight/obese individuals facing joint pain and Middle-aged adults looking forward to keep joint health.

Calcium, magnesium, vitamin D, chondroitin, glucosamine, vitamin K, collagen, or even fatty acids and hyaluronic acid are among the most popular ingredients with scientific studies that support bone and joint health benefits. Strongly science backed and highly bioavailable ingredients are essential when formulating a bone and joint care product. As a result, products expect to gain market shares with solid science and clinical data. This article summarizes the mechanisms of oral hyaluronic acid to promote joint health as well as providing the latest clinical studies.



1. Introduction

1.2 The Beauty Supplements Market driven by changing lifestyle and increasing consumer incomes

Lifestyle change and increase of economy have boosted global sales of beauty supplements. Global beauty supplements market accounted for USD 3.5 Billion in 2016 and the market is expected to reach USD 7.1 Billion by the end of 2023, growing at a Compound Annual Growth Rate (CAGR) of 9.5%. Based on applications, the global beauty supplements market is segmented into skin care, haircare, nail care, dental care and other (overall health supplements) applications. In 2016, skin care supplements accounted for the largest share of more than 30% of the total global beauty supplements market by value.

Geographically, the global beauty supplements market is segmented into North America, Europe, Asia Pacific, Latin America and Middle East & Africa regions. Asia-Pacific accounted for the highest share in global beauty supplements market and is expected to dominate the market over the forecast period. Japan is the largest market in Asia for beauty supplements closely followed by China and Korea. Europe is the second largest market with more than 25% share in global beauty supplements market. Western Europe (Germany, U.K., Spain, Italy and France) accounted for major revenue share of more than 20% in global beauty supplements market. Europe beauty supplements market is majorly driven by the rising consumer concerns towards their health and their beauty appearance. North America is the third largest market owing to high disposable income and rising endorsement by celebrities.

Vitamin A, C, D and E, Fish Oil, Hyaluronic Acid, Collagen, Coenzyme Q10 are among the most popular ingredients with scientific studies that support beauty benefits. This article summarizes the mechanisms behind beauty effects of hyaluronic acid for beauty effects as well as providing the latest clinical studies.

1. Introduction

1.3 What is hyaluronic acid and HAPLEX® Plus?

Hyaluronic acid holding up the body

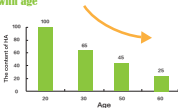
Hyaluronic acid (HA) is a kind of polysaccharide composed of repeating disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine^[2]. Sodium hyaluronate is the sodium salt form and is also the commercial form of HA. It is a substance found in all vertebrates, mainly in connective tissues such as cartilage, bone, skin etc.^[3] Concentrations (ug/g) of HA in various organs of different species are listed below^[4]. Because of its unique physical and chemical properties, HA plays an important role in facilitating smooth movement of the knee joint, maintaining the normal shape of the vitreous humor, and moisturizing the skin.

Organ or fluid	Man	Sheep	Rabbit	Rat
Umbilical cord	4100			
Synovial fluid	1400-3600	540	3890	
Dermis	200			
Vitreous body	140-338	260	29	
Lung		98-243		34
Kidneys			93-113	30
Renal papillae			250	
Renal cortex			4	
Brain	35-115		54-76	74
Muscle			27	
Intestine				44
Thoracic lymph	8.5-18	1-34		5.4
Liver			1.5	4
Aqueous humour	0.3-2.2	1.6-5.4	0.6-2.5	0.2
Urine	0.1-0.3			
Lumbar CSF	0.02-0.32			
Plasma (serum)	0.01-0.1	0.12-0.31	0.019-0.086	0.048-0.26

1. Introduction

HA content in the body decreases with age

As people getting aged, the metabolism of cells slows down and HA synthesis in our body decrease. As a result, there is no enough HA in the synovial fluid of joints for lubrication and no enough HA in the skin for water retention.



HA content in the body decreases with age
(Longes MO, Russell CS, He X-Y., 1987)

What is HAPLEX® Plus?

HAPLEX® Plus, high quality food grade Sodium Hyaluronate, was the first one approved in China as a New Dietary Ingredient. Clinical studies shows that HAPLEX® Plus could promote joint health and skin beauty.

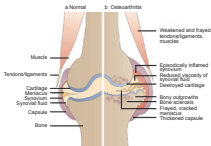


2. HAPLEX® Plus

2.1 How hyaluronic acid could promote joint health?

Osteoarthritis (OA) is a type of joint disease that results from breakdown of joint cartilage and underlying bone^[2]. The most common symptoms are joint pain and stiffness. Initially, symptoms may occur only following exercise, but over the time may become constant.

HA has high viscosity and elasticity in water. The viscosity of synovial fluid is attributable to HA and HA serves as a lubricant for joint movements. Studies find that the content of HA in synovial fluid of OA Patients will decline^[3]. There is a large agreement that early manifestations of OA are related to changes in the viscoelasticity of the synovial fluid which account for a decrease in the protective action of the cartilage: such deterioration appears mainly due to a decrease in the concentration and molecular weight of synovial HA. Beside this, the functions of HA include preventing cartilage



Other symptoms may include joint swelling, decreased range of motion, and when the back is affected weakness or numbness of the arms and legs. Although OA occurs in people of all ages, it is most common in people older than 65. Common risk factors include increasing age, obesity, previous joint injury, overuse of the joint, weak thigh muscles, and genes.



denaturation^[7, 8], protecting the outer layer of cartilage^[9, 10], blocking synovial inflammation^[11], increasing chondrocyte density^[12], promoting synovium metabolism^[13], normalizing synovial fluid^[14], and relieving pain^[15]. Therefore, HA is known to have a strong relationship with knee joint health.

2. HAPLEX[®] Plus

2.2 Why you should use hyaluronic acid in your formulations?

Chondroitin and glucosamine are the most popular ingredients that support bone and joint health. A lot of studies have confirmed that chondroitin sulfate, glucosamine and hyaluronic acid play different roles in joints, and they synergistically promote joint health. Due to the key role of hyaluronic acid in joint health, joint care supplements with hyaluronic acid are becoming more and more popular, and hyaluronic acid has become an essential ingredient for joint health products. Our company has carried out clinical trials of oral chondroitin sulfate and hyaluronic acid to improve the symptoms of degenerative OA, and the improvement effect is very obvious.



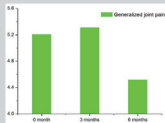
2. HAPLEX® Plus

2.3 What kind of benefits that HAPLEX® Plus could bring for joint health?

1

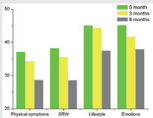
Title:	<i>Clinical study on the efficacy of HAPLEX® Plus associated with Chondroitin Sulfate (CS) in the symptomatic treatment of degenerative OA</i>
Research organization:	<i>A&G laboratories, Spain</i>
Samples:	<i>HAPLEX® Plus (Bloomage Biotechnology Corporation Limited) 150mg/day, CS 800mg/day</i>
Volunteers:	<i>N=29, age 40–80, diagnosis of knee osteoarthritis;</i>
Method:	<i>The study of HAPLEX® Plus associated with CS was designed, organized and implemented as a prospective clinical study of 6 months follow up. The 29 volunteers were assigned to one treatment group. Follow-up visits were scheduled in the research laboratory at 3 and 6 months of starting treatment. The efficiency of the treatment was expressed for the following parameters: generalized joint pain intensity using visual analogue scale (VAS) from 0 to 10, WOSI index of shoulder instability, WOMAC questionnaire for knee and hip OA, Lequesne index for knee OA.</i>

Results:

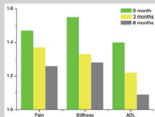


- Changes in the intensity of generalized joint pain were assessed at each visit with the score, using the Likert scale. The Likert scale evaluates 0 (No pain) and 10 (Maximum pain).
- The mean intensity of generalized joint pain was reduced by an average of 0.69 units ($p < 0.05$).
- The symptom is improved after the study.

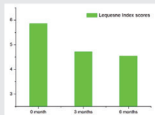
2. HAPLEX® Plus



- The WOSI questionnaire has four parts, namely Physical symptoms, Sports/Recreation/Work (SRW), Lifestyle and Emotions. Score 0 represents lightest symptom, whereas score 100 represents the severest symptom for each variable.
- The scores decreased significantly after the study. Physical symptoms, SRW, Lifestyle, $p < 0.01$; Emotions $p < 0.05$.
- The symptom is improved after the study.



- The WOMAC questionnaire has three parts, namely Pain, Stiffness and Activities of Daily Living (ADL). Score 0 represents lightest symptom, whereas score 4 represents the severest symptom.
- The Pain, Stiffness and ADL Scores decreased significantly after the study. Pain, ADL $p < 0.01$; Stiffness $p < 0.05$.
- The symptom is improved after the study.



- Assessment at each time point was made according to the scoring of Lequesne algofunctional index. Score 0 represents lightest symptom, whereas high score represents the severest symptom for each questionnaire.
- The score decreased significantly ($p < 0.01$) and the symptom is improved after the study.

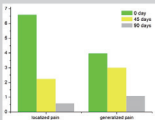
Conclusion: Oral administration of HAPLEX® Plus and CS can improve the symptoms of the OA.

2. HAPLEX® Plus

2

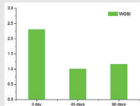
Title:	<i>Clinical study on the efficacy of HAPLEX® Plus in the improvement of the articular cartilage for people who practice intense physical activity</i>
Research organization:	<i>A&G laboratories, Spain</i>
Samples:	<i>HAPLEX® Plus (Bloomage Biotechnology Corporation Limited) 150mg/day</i>
Volunteers:	<i>N=33, Perform very intense physical activity;</i>
Method:	<i>The study of HAPLEX® Plus was designed, organized and implemented as a prospective clinical study. The 33 volunteers treated with HAPLEX® Plus for 90 days. The efficiency of the treatment was expressed for the following parameters: Visual Analogue Scale localized pain and general pain, WOSI index of shoulder instability, WOMAC questionnaire for osteoarthritis of the knee and hip, Lequesne index for knee OA.</i>

Results:

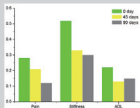


- The pain was evaluated in each visit with the score using the Likert scale. The Likert scale was scored 0 (No pain) and 10 (Maximum pain).
- The average intensity of localized pain and generalized pain were reduced by an average of 4.50 and 2.90 units, which were both statistically significant ($p < 0.001$) and clinically relevant.
- The symptom is improved after the study.

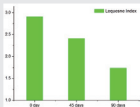
2. HAPLEX® Plus



- The WOSI questionnaire has four parts, namely Physical symptoms, Sports/Recreation/Work (SRW), Lifestyle and Emotions. Score 0 represents lightest symptom, whereas score 100 represents the severest symptom for each variable.
- There are statistically significant differences between the baseline and the final ($p=0.003$).
- The symptom is improved after the study.



- The WOMAC questionnaire has three parts, namely Pain, Stiffness and Activities of Daily Living (ADL). Score 0 represents lightest symptom, whereas score 4 represents the severest symptom.
- The Pain, Stiffness and ADL Scores decreased significantly after the treatment. The symptom is improved after the study.



- Assessment at each time point was made according to the scoring of Lequesne algofunctional index. Score 0 represents lightest symptom, whereas high score represents the severest symptom for each questionnaire.
- The score decreased significantly and the symptom is improved after the study.

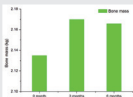
Conclusion: In this study, it is observed that the pain suffered by the volunteers is relieved and the functionality of their articular cartilage is significantly improved. Oral administration of HAPLEX® Plus can improve joint health.

2. HAPLEX® Plus

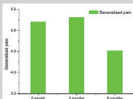
3

Title:	<i>Clinical study on the efficacy of HAPLEX® Plus in the improvement of osteoporosis</i>
Research organization:	<i>A&G laboratories, Spain</i>
Samples:	<i>HAPLEX® Plus (Bloomage Biotechnology Corporation Limited) 150mg/day</i>
Volunteers:	<i>N=29, age 55-79, with osteoporosis;</i>
Method:	<i>The study of HAPLEX® Plus was designed, organized and implemented as a prospective clinical study. The 33 volunteers were treated with HAPLEX® Plus for 6 months. The efficiency of the treatment was expressed for the following parameters: the rate of bone transmission, VAS general pain.</i>

Results:



- The bone mass increased at an average of 0.031 unit ($p = 0.010$).
- The symptom is improved after the study.



- The average intensity of generalized pain reduced by an average of 0.69 unit ($p = 0.023$).
- The symptom is improved after the study.

Conclusion: *In this study, it is observed that the osteoporosis of postmenopausal women is improved. Oral administration of HAPLEX® Plus is proved to be effective, with statistically significant results on the bone mass and generalized pain.*

3. HAPLEX® Plus

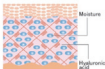
3.1 How hyaluronic acid could promote skin beauty

The skin is the largest organ of the body, and it acts as a barrier protecting against exogenous factors and preventing water loss from the body. Dry skin can reduce skin barrier function. Dry skin also can reduce a person's quality of life not only because of itching but also the discomfort associated with tight and dry skin. Moreover, dry skin also contributes to the formation of wrinkles.

HA exists in all vertebrates, mainly in skin, cartilage, bone etc. In particular, more than 50% of total body HA is present in the skin^[16, 17]. The HA content of the dermis is far greater than that of the epidermis^[18]. HA plays a major role in maintaining extracellular spaces, preserving tissue hydration and facilitating the transport of ion solutes and nutrients to cells in the upper layer because of its water-retaining capacity. Therefore, HA is important for maintaining healthy skin. However, aging and extrinsic stimuli such as solar ultraviolet radiation, smoking, and air pollutants gradually reduces the amount of HA in the body. The reduction of HA in the body increase joint pain and dry skin. In recent years, the public has started to ingest HA to compensate for its loss in the body. HA dietary supplements are expected to be effective anti-aging supplements because an American ABC News program, which aired in November 2002, stated that the key to longevity in a specific Japanese village was their HA-rich diet^[19].

Anti-Aging

- Skin with high hyaluronic acid content



- Skin with low hyaluronic acid content



3. HAPLEX® Plus

3.2 Why you should use HA in your formulations?

Collagen is widely used in beauty dietary supplements. If hyaluronic acid is added to the formula, will it work better? The answer is of course yes.

HYALURONIC ACID + COLLAGEN = THE DREAM TEAM

Just like best friends who are so close that they finish each other's sentences, HA and collagen complement and support one another perfectly. HA enhances the body's ability to produce and synthesize, or use of collagen. By taking collagen and HA together, you're increasing the efficacy of both. Which leads to global benefits for your entire system.

Collagen is a natural structural protein in a fibrous form found in a human's body. Around 30% of all body proteins are collagen. Specifically relevant to skin, collagen provides strength, flexibility and resistance. In another words, it's the presence of collagen that gives skin firmness. HA molecules can retain up to 1000 times its weight in water. Therefore, HA's secret is keeping the skin moisturised and hydrated. HA works with

collagen by providing a moisture rich environment where collagen can stretch without breaking. While Collagen works on the skin firmness, HA nourishes and hydrates the Collagen to keep it supple and flexible, filling the free space of the skin matrix with water and giving it a fuller, firmer and youthful appearance. HA also helps with wound healing, tissue repair, chapped lips, dry scalp issues, gums and even the moisture level of our eyes. So formula with HA could bring a perfect result of 1+1>2.



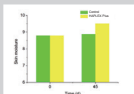
3. HAPLEX® Plus

3.3 What kind of benefits that HAPLEX® Plus could bring for skin beauty?

1

Title:	<i>Clinical study on the skin moisturizing efficacy of HAPLEX®Plus</i>
Research organization:	<i>Health food registered inspection agency, China</i>
Samples:	<i>HAPLEX® Plus (Bloomage Biotechnology Corporation Limited) 120mg/day and placebo capsules</i>
Volunteers:	<i>N=52, aged 30~50, female</i>
Method:	<i>The study of HAPLEX®Plus was designed, organized and implemented as a prospective clinical study. The 52 volunteers were treated with HAPLEX®Plus and placebo for 45 days respectively. The forehead skin moisture and safety items were tested in the study.</i>

Results:



- The skin moisture of test group increased from 8.8 to 9.5, the difference was significant ($p < 0.05$). The difference between the test group and the control group was significant ($p < 0.05$).
- The skin moisture of the test group is increased after the study.

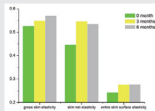
3. HAPLEX® Plus

2

Title:	Clinical study on the anti-wrinkle efficacy of HAPLEX® Plus
Research organization:	A&G laboratories, Spain
Samples:	HAPLEX® Plus (Bloomage Biotechnology Corporation Limited) 150mg/day
Volunteers:	N=29

Method: The study of HAPLEX® Plus was designed, organized and implemented as a prospective clinical study. The 29 volunteers were treated with HAPLEX® Plus for 6 months. The efficiency of the treatment was expressed for the following parameters: gross skin elasticity, skin net elasticity and entire skin surface elasticity.

Results:



- The mean gross skin elasticity, skin net elasticity and entire skin surface elasticity increased by an average of 0.04 unit (7%), 0.04 unit (15%) and 0.03 unit (11%), which were all statistically significant and clinically relevant.
- The symptom is improved after the treatment.

Conclusion: Oral HAPLEX® Plus is proved to be effective, with statistically significant results on the parameters of skin moisture and skin elasticity. Oral administration of HAPLEX® Plus can nourish skin from within and make it more elastic.

Conclusions

4. Conclusions



Nowadays, people are living longer and heavier, and more and more people are suffering joint problems. HA used as a dietary supplement ingredient is safe with no side effects. The efficacy of oral HA in promoting joint health and skin beauty was demonstrated by the clinical trials. Meanwhile oral HA can promote the



Conclusions



health of eyes, mucosa, etc. More researches are still needed. This article help people to understand more on HA and its benefits.

5. Why us?

TOP 5 REASONS

1 Clinically proved benefits

Your product deserves the best ingredients. HAPLEX® Plus has clinically proved benefits for joint health and beauty from within.

2 Natural, Safe

Produced by fermentation, HAPLEX® Plus is Kosher and Halal certified, non-GMO and non-animal origin. The safety of HAPLEX® Plus is proved by American and Chinese authoritative testing agency.

3 High purity

HAPLEX® Plus is with higher assay and lower impurities.

4 Strict quality management syement

With ISO9001, HACCP, ISO22000 and GMP quality management system, the quality of HAPLEX® Plus can be assured.

5 Professional service

Bloomage Biotechnology is the largest Sodium Hyaluronate manufacturer in the world. With more than 20 years' experience, we can provide our valued partners with customized products and all-around technical support related to hyaluronic acid application.

BLOOMAGE BIOTECHNOLOGY CORPORATION LIMITED

Add: No.678 Tianchen St., High - Tech Development Zone, Jinan, China 250101

Tel: +86 531 82685998 Fax: +86 531 82685988

www.bloomagebioactive.com E-mail: customer@bloomagebioactive.com

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