

This white paper will outline the status of joint care market and the clinical data of HAPLEX® Plus promoting joint health.

**Top ingredient for
joint care
HAPLEX® Plus**

Natural, Safe, Efficacy Tested



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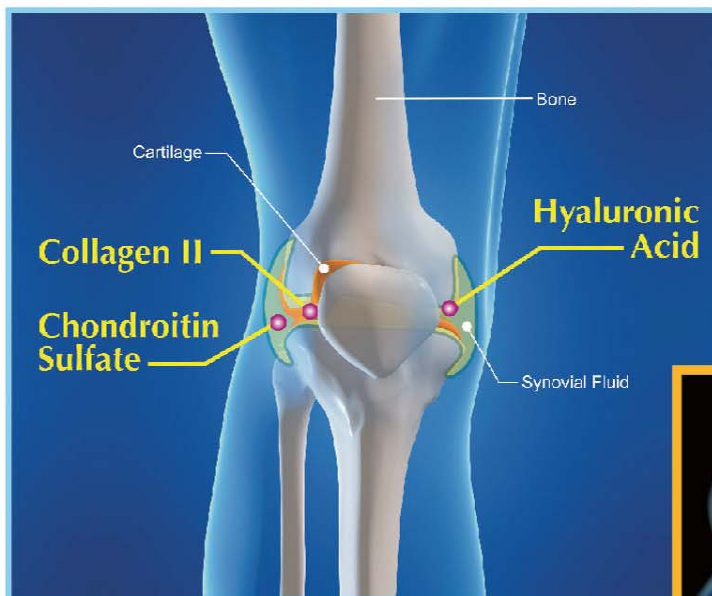


1. Introduction

People around the world are living longer and heavier. All your 360 joints are taking the load for the lifetime of all your activities. The number of patients with osteoarthritis (OA) is increasing all over the world. As humans getting older, their joint tissues follow suit. The World Health Organization (WHO) mentions that OA is affecting approximately one-third of those aged 65 and older. In the United States, the number of patients with OA is projected to grow to more than 60 million by 2020^[1].

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 time may become constant. 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.



1. Introduction



Severe OA is treated by osteotomy or artificial joint replacement, whereas conservative treatments include intra-articular injection of sodium hyaluronate(HA) [3]. The injections improve symptoms, although they represent a mental burden and the risk of infection for patients who need to visit the hospital regularly to receive these painful injections. Meanwhile, dietary supplements such as HA, glucosamine, and chondroitin sulfate are targeting problems with the OA. These natural supplements are safe, effective and of low-cost.

Global Industry Analysts predicted the bone and joint supplements market to reach USD \$9 billion 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 to proactively preserve joint health.

Due to the complex need, many joint health ingredients target three main areas- promoting healthy joint tissues, protecting against inflammation and relieving pain. Compared to these ingredients, HA tackles all three mechanisms of action. This article summarizes the mechanisms of oral HA to promote joint health as well as providing the latest clinical studies of HAPLEX® Plus.



2. HAPLEX® Plus



2.1 What is HAPLEX® Plus?

Sodium Hyaluronate (Hyaluronic Acid, HA) is a high molecular-weight polysaccharide composed of repeating disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine^[4]. In human beings, HA is present in connective tissues and organs such as skin, synovial fluid, cartilage, blood vessels, heart valves and so on^[5]. Normal concentrations (ug/g) of HA in various organs of different species are listed below^[6]. HAPLEX® Plus is a Food Chemicals Codex (FCC) grade Sodium Hyaluronate with higher purity and tested efficacy.

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



2. HAPLEX® Plus

2.2 Mechanisms of oral HAPLEX® Plus for joint care

HA has high viscosity and elasticity in water. The viscosity of synovial fluid is attributable to HA and HA works as a lubricant for joint movements. The content of HA in synovial fluid of OA Patients will decline^[7]. The functions of HA include preventing cartilage denaturation^[8, 9], protecting the outer layer of cartilage^[10, 11], blocking synovial inflammation^[12], increasing chondrocyte density^[13], promoting synovium metabolism^[14], normalizing synovial fluid^[15], and relieving pain^[16]. So HA is of great benefits for joint health.



3. Clinical Studies

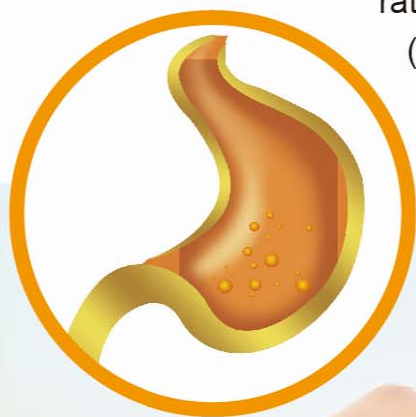


3.1 Oral absorption of HA

The synthesis and degradation of HA in the body is a dynamic balanced process. It is proved by numerous studies that oral intake of HA can increase the precursors of HA and promote the synthesis of HA. Balogh et al. reported that ^{99m} technetium-labeled HA (MW, 1.1-1.5MDa) is found in tissues such as joints and skin after oral administration in rats and dogs and the result is different from the control group [17]. Jiang Qiuyan et al. made the

rats taken HA solution (MW, 0.9-1.3 MDa; HAPLEX[®],

Bloomage Freda Biopharm Co., Ltd., China). The concentration of the HA in the serum appears an apparent peak value at around 2 hours, drops during 2-4 hours, and appears tendency of steady increase during 4-13 hours. In around 2 hours, the organism can absorb the exogenous HA in the form of non-monosaccharides, showing a rapid increase of blood drug level. After it was degraded and absorbed, new HA was synthesized, resulting in steady rise of blood drug level in around 6 to 13 hours. All these studies clearly illustrate that oral HA can be absorbed by the body.



3. Clinical Studies



3.2 Clinical studies of oral HAPLEX® Plus for joint care

1

Title: *Clinical study on the efficacy of HAPLEX® Plus associated with Chondroitin Sulfate (CS) in the symptomatic treatment of degenerative OA*

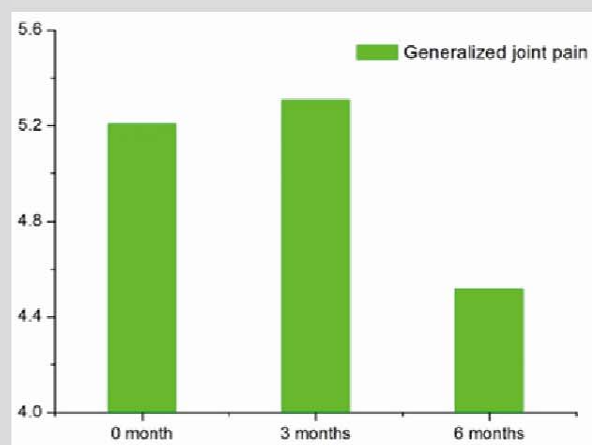
Research organization: *A&G laboratories, Spain*

Samples: *HAPLEX® Plus (Bloomage Freda Biopharm Co., Ltd.)
150mg/day, CS 800mg/day*

Volunteers: *N=29, age 40~80, diagnosis of knee osteoarthritis;*

Method: *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.*

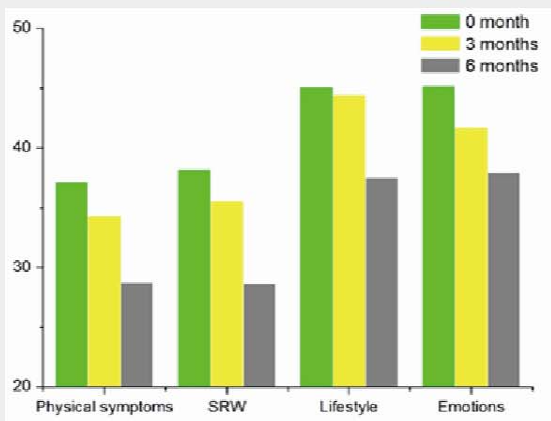
Results:



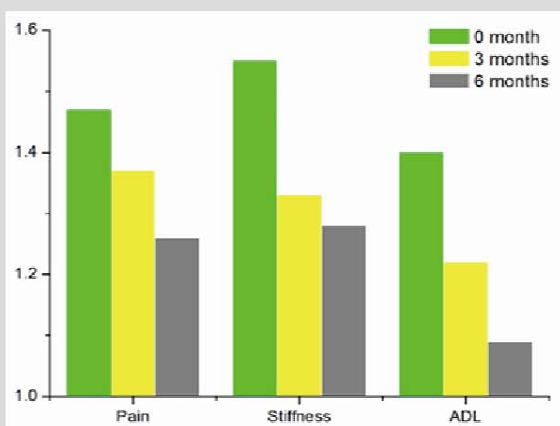
- *Changes in the intensity of generalized joint pain were assessed at each visit with the score, using the Likert scale. The Likert scale evaluates 0 (No pain) and 10 (Maximum pain).*
- *The mean intensity of generalized joint pain was reduced by an average of 0.69 units ($p < 0.05$)*
- *The symptom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

Clinical

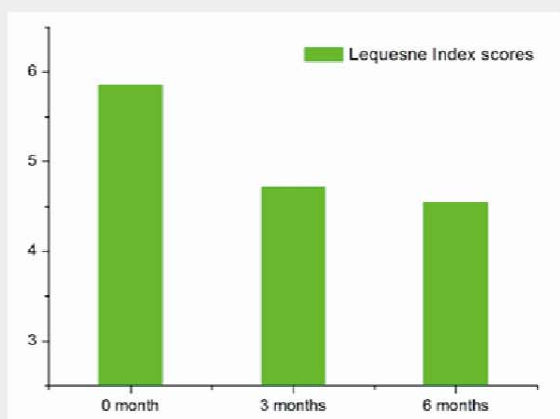
3. Clinical Studies



- 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 help to improve the symptoms of the OA. The dose of CS is below the therapeutic level, which is most probably insignificant, and therefore we can conclude that the effectiveness in this study is mainly from HAPLEX® Plus.

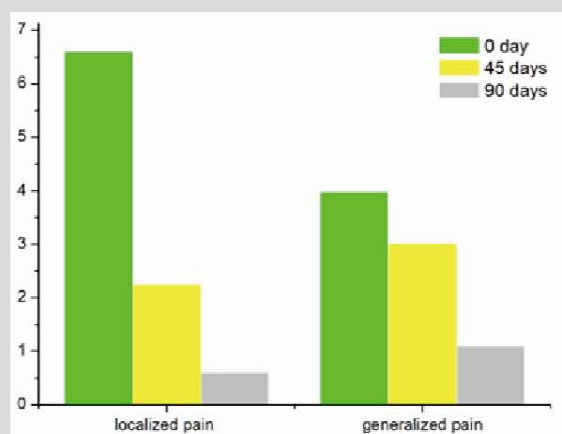
3. Clinical Studies



2

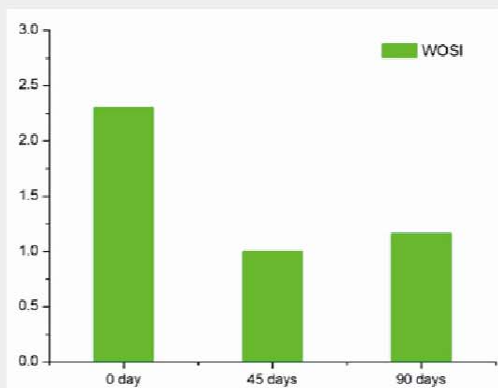
Title:	<i>Clinical study on the efficacy of HAPLEX® Plus in the improvement of the articular cartilage for people who practice intense physical activity</i>
Research organization:	<i>A&G laboratories, Spain</i>
Samples:	<i>HAPLEX® Plus (Bloomage Freda Biopharm Co., Ltd.) 150mg/day</i>
Volunteers:	<i>N=33, 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:

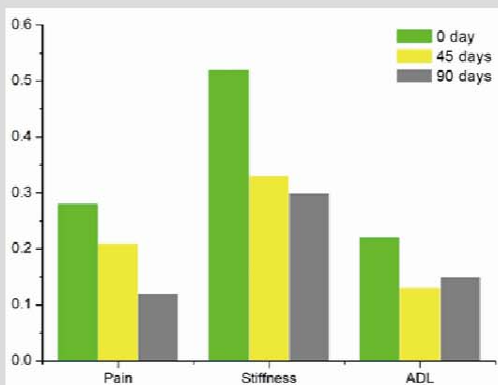


- *The pain was evaluated in each visit with the score using the Likert scale. The Likert scale was scored 0 (No pain) and 10 (Maximum pain).*
- *The average intensity of localized pain and generalized pain were reduced by an average of 4.50 and 2.90 units, which were both statistically significant ($p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

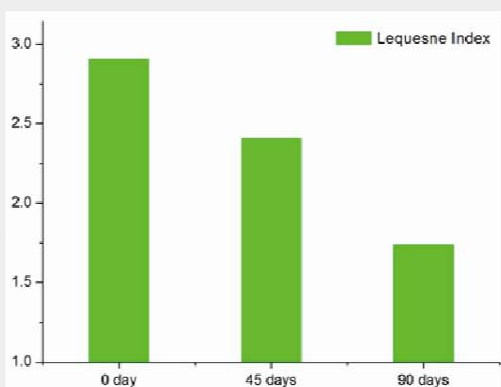
3. Clinical Studies



- 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.*



3. Clinical Studies

3

Title: *Clinical study on the efficacy of HAPLEX® Plus in the improvement of osteoporosis*

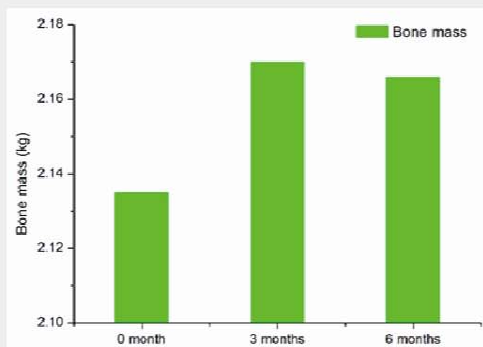
Research organization: *A&G laboratories, Spain*

Samples: *HAPLEX® Plus (Bloomage Freda Biopharm Co., Ltd.) 150mg/day*

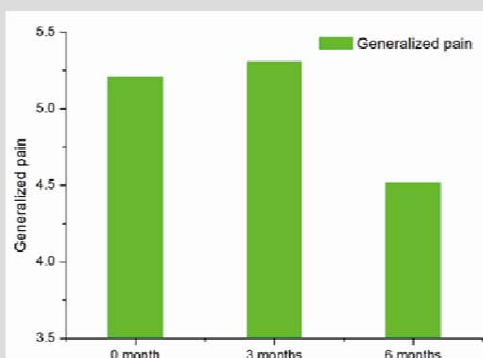
Volunteers: *N=29, age 55-79, with osteoporosis;*

Method: *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.*

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.*

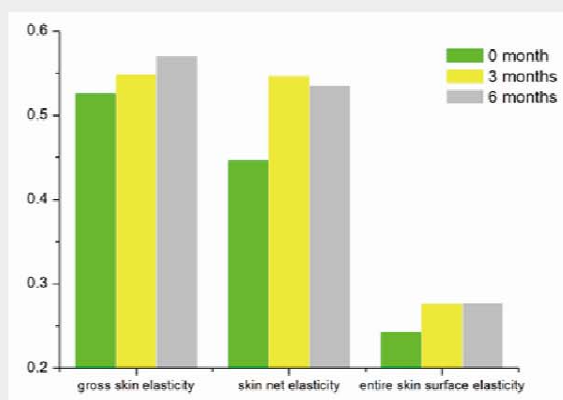
3. Clinical Studies



3.3 Clinical studies of oral HAPLEX® Plus for anti-wrinkle

Title:	<i>Clinical study on the anti-wrinkle efficacy of HAPLEX® Plus</i>
Research organization:	<i>A&G laboratories, Spain</i>
Samples:	<i>HAPLEX® Plus (Bloomage Freda Biopharm Co., Ltd.) 150mg/day</i>
Volunteers:	<i>N=29</i>
Method:	<i>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.</i>

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.*

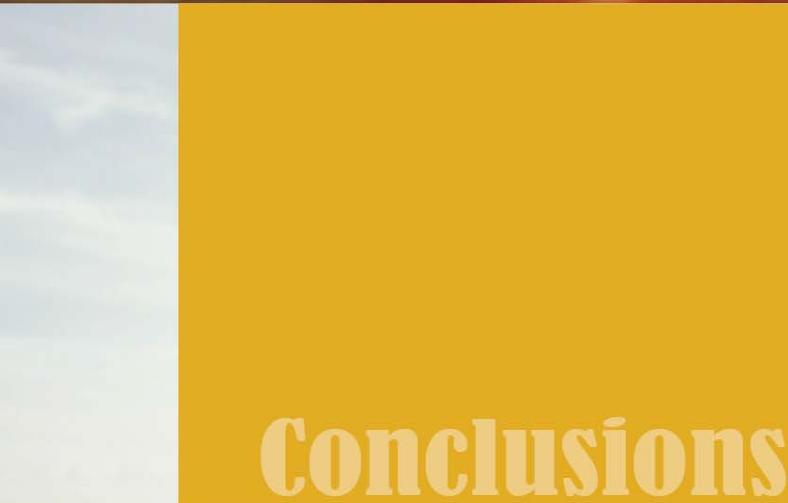
Conclusion: *Oral HAPLEX® Plus is proved to be effective, with statistically significant results on the parameters of skin elasticity. Oral administration of HAPLEX® Plus can nourish skin from within and make it more elastic.*

Conclusions

4. Conclusions



Currently people are living longer and heavier. People with joint problems are becoming more and more. HA used as a dietary supplement ingredient is safe and with no side effects. The efficacy of oral HA in promoting joint health was demonstrated by a lot of clinical trials. In addition to promoting joint



health, oral HA can also promote the health of skin, eyes, mucosa and so on. This article help people to understand more on HA and its benefits.

Why us

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

3 High quality

HAPLEX® Plus is with higher assay and lower impurities.

4 High stability

With ISO 9001 and GMP quality system, the stability and reliability of HAPLEX® Plus can be assured.

5 Professional service

Bloomage Freda is the largest Sodium Hyaluronate manufacturer in the world. With more than 20 years' experience, Bloomage Freda can provide you with customized products and all-around technical support for HAPLEX® Plus application.

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