artilane®

ARTILANE®: The drinking vial for healthy joints.

Hyaluronic Acid · Hydrolysed Collagen · Anti-oxidants

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Product information

1 Absorption and effects of orally administered hyaluronic acid

Hyaluronic acid (HA) is "absorbed" in a human intestinal tract model.

Monolayer arrangements of human intestinal cells (Caco-2 cells) are used for ex-vivo examination of the absorption mechanisms of drugs. It was demonstrated in this model that "low-molecular-weight" HA is absorbed, depending on the quantity administered and the molecular weight of the substance. Absorption occurs via a paracellular mechanism. The investigators point out that the amount of HA absorbed in the human body is probably higher than in the study, since a human small intestinal epithelium at 50 ohm/cm^2 exhibits a markedly lower diffusion resistance than the model, which because of the higher cell density had a resistance of more than 500 ohm/cm^2.

Hisada N et al. Low-Molecular-Weight Hyaluronan Permeates through Human Intestinal Caco-2 Cell Monolayers via the Paracellular Way, Biosci Biotechnol Biochem 2008; 72 (4): 1111–1114.

Labeled hyaluronic acid appears in organs and joints of rats and dogs after oral administration.

Wistar rats and Beagle dogs received a single oral dose of 200 mcg and 10 mg HA, respectively, labeled with technetium-99-pertechnetate. Seventy-two hours after administration of the substance, only 5 % of the marker had been excreted in the stool. Within 30 minutes of oral administration of the substance, marker signals were found in the animals' blood, muscles, salivary glands and bones; peak concentrations were reached after 4–6 hours. Radioactivity was measured in the shoulder joint and vertebral column 4 hours after administration. It was shown that HA is absorbed after a single oral administration and can be detected in animals' organs and joints.

Schauss AG et al. Absorption, distribution and excretion of 99m-technetium labeled hyaluronan after single oral doses in rats and beagle dogs, Conference on Experimental Biology 2004; Abstract 129.4.

Oral hyaluronic acid induces a sustained increase in HA serum concentrations in rats.

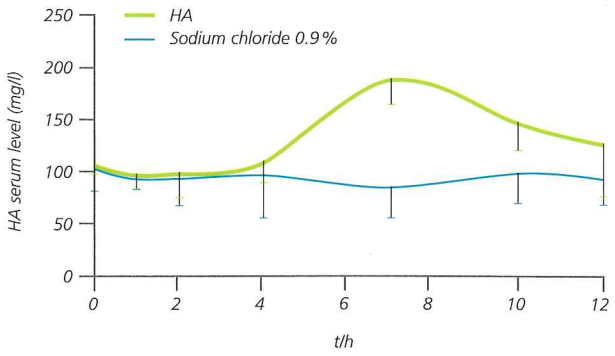
In a study of the absorption-promoting effect of phospholipids on HA uptake after oral administration to rats, a marked increase in HA concentration was detected in the serum even after administration of HA alone. Serum HA concentrations in rats vary generally between 46–240 mg/L. Therefore only animals with baseline serum concentrations of less than 180 mg/L were included in the study and these received 60 mg/kg BW HA orally. Serum HA concentrations were determined by a specific radioimmunoassay (RIA). Four hours after administration an increase in HA serum levels was seen, which had not fully reverted to the baseline value by the end of the study (12 hours after administration of HA). The marked increase in HA concentrations over time was seen in the analysis of the total bioavailability (by the area under the curve/AUC procedure) of 381.1±340.8 ng·h/ml.

Huang SL et al. Oral absorption of hyaluronic acid and phospholipids complexes in rats, World J Gastroenterol 2007; 13 (6): 945–949.

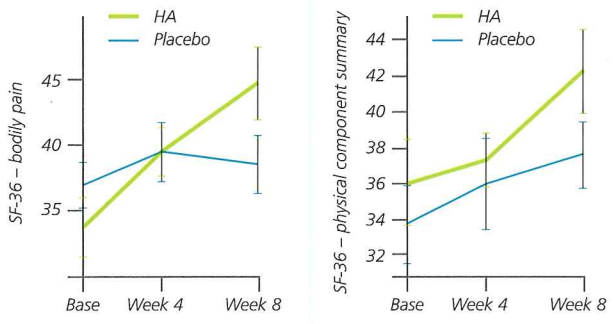
Oral hyaluronic acid improves bone metabolism and bone architecture in rats with estrogen deficiency.

Surgical removal of the ovaries (OVX) in rats causes estrogen deficiency and consequently results in an artificial postmenopause. Biochemical markers for bone resorption (increase in deoxypyrolidine/DPyr and pyrolidine/Pyr) are then found in the urine, while a decrease in serum NO, a marker for bone formation, is

Time course of HA serum levels after oral administration (according to Huang SL et al., 2007)



Marked improvement of the SF-36-parameters "bodily pain" and "physical component summary" after 8 weeks of treatment with oral HA (Kalman DS et al., 2008)



reflected in reduced nitrite/nitrate values. Estrogen deficiency also causes a reduction in bone mineral density, BMD. The investigators compared the effect of oral HA with a molecular weight of 0.75 million dalton (in a daily dose of 1 mg/kg BW) and of 1.62 million dalton (in daily doses of 0.5 and 1 mg/kg BW) on these markers in rats after ovariectomy with that in animals in which ovariectomy was merely simulated (sham). On Day 28 serum concentrations of DPyr and Pyr in animals treated with high-molecular-weight HA were significantly above those of the OVX group and in the range of the sham group. A significant increase in serum NO values was obtained in all treatment groups, while a significant increase in BMD in the whole skeleton and femur of the animals was only found with the higher dose of high-molecular-weight HA.

Stancikova M et al. The effects of hyaluronan on bone resorption and bone mineral density in a rat model of estrogen deficiency-induced osteopenia, Int J Tissue React 2004; XXVI (1/2): 9–16.

Oral hyaluronic acid reduces joint effusion in young thoroughbred horses after arthroscopy of the tarsocrural joint.

Unilateral or bilateral osteochondritis dissecans of the tarsocrural joint (and other joints) is not uncommon in young thoroughbred horses. Arthroscopic debridement prevents a degenerative joint disease and safeguards the horse's performance. In a controlled double-blind study 24 horses (27 joints) were administered orally a dose of gel containing 100 mg HA for a period of 30 days postoperatively, while animals in the control group (24 horses, 30 joints) were treated with a placebo gel. Thirty days after arthroscopy a neutral investigator assessed the extent of any joint effusion on the dorsomedial side of the joint. The five-point ordinal scale ranged from 0 = no effusion to 5 = more than tennis ball-sized effusion with plantar extension. The mean score for joint effusion on Day 30 after arthroscopy was 0.67 in the HA group, but 2.05 in the placebo group ($p \leq 0.0001$). This study shows that oral HA reduces postoperative joint effusion after arthroscopic debridement of the tarsocrural joint in the horse.

Bergin BJ et al. Oral hyaluronan gel reduces post operative tarsocrural effusion in the yearling Thoroughbred, Equine Veterinary Journal 2006; 38 (4): 375–378.

A pilot study provides evidence of the benefit of oral hyaluronic acid in patients with osteoarthritis of the knee.

A total of 20 patients with knee osteoarthritis were included in a controlled double-blind study of the efficacy and safety of oral HA. Ten patients received oral HA (at a dose of 50 mg daily) over a period of 8 weeks and a further ten patients a placebo of identical appearance. The WOMAC Index and the SF-36v2 short version of the quality of life were used before and 4 and 8 weeks after the beginning of treatment to record the findings. Because of the small number of patients and the resultant high standard deviation, group differences were difficult to demonstrate statistically. Numerical superiority of the HA treatment, however, was found in the WOMAC for physical functioning and total score and in the SF-36v2 for physical pain. The high consumption of permitted analgesics (capsules of 500 mg paracetamol) in the placebo group is striking, averaging 6.8 capsules per week in the first four weeks, as against only 3.1 capsules in the HA group.

Kalman DS et al. Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint®) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial. Nutrition Journal 2008; 7: 3.

2 Protective effects of hydrolysed collagen

The role of hydrolysed collagen in osteoarthritis and osteoporosis

is assessed positively by Moskowitz, one of the leading rheumatologists in the United States. Hydrolysed collagen has long been used in drugs and food supplements and the licensing authorities generally rate these products as safe. Collagen hydrolysate of pharmaceutical quality (PCH) is obtained by hydrolysis of pharmaceutical gelatine. Clinical studies show a daily intake of 10 g to be advisable. The predominantly gastro-intestinal side effects that occur (such as a feeling of fullness or unpleasant taste) are negligible. A multicentre, randomised, placebo-controlled, double-blind study with centres in the USA, UK and Germany revealed a statistically significant superiority in the parameter of pain in the German centres. Patients with more severe symptoms at the beginning of the study exhibited a better response. ^{14}C-labeled substance accumulates predominantly in joint cartilage, where it can exert beneficial effects on cartilage metabolism and anabolism. As collagen is also very important for bone structure, the effect on bone metabolism of osteoporosis patients was also studied. Studies in which the effects of calcitonin were compared with those of calcitonin plus collagen show that the combination inhibits collagen degradation in the bones more strongly than calcitonin alone. Collagen hydrolysate is therefore beneficial in the treatment of osteo-arthritis and osteoporosis, while its safety allows prolonged use in these chronic diseases.

Moskowitz RW. Role of collagen hydrolysate in bone and joint disease. Semin Arthritis Rheum 2000; 30 (2): 87–99.

Evidence of safety and efficacy of collagen hydrolysate in joint diseases.

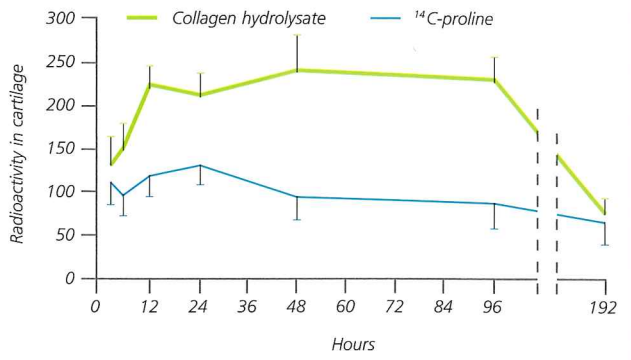
As millions of people in the United States suffer from osteoarthritis, there is an urgent need for an effective treatment option. As a result of the ageing of the population, the need for traditional and non-traditional treatment procedures will increase further. This article reviews the information available on a particular substance, collagen hydrolysate, in medical databases and other sources using appropriate search terms. Published data confirm that orally administered collagen hydrolysate is absorbed and accumulates in joint cartilage. Compared to untreated controls, collagen hydrolysate causes a statistically significant increase in the synthesis of extracellular matrix macromolecules by chondrocytes. This finding points to mechanisms which may also be beneficial for patients with joint diseases, such as osteoarthritis. Four open-label and five double-blind studies were found and analysed in the research. They show collagen hydrolysate to be safe and an option for less pain and better joint function in patients with OA or other joint diseases.

Bello AE, Oesser S. Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature, Curr Med Res Opin 2006; 22 (11): 2221–2232.

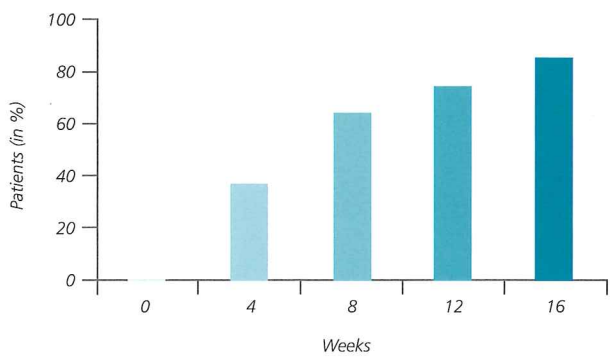
Collagen hydrolysate stimulates collagen II production by chondrocytes in vitro, while native collagen remains ineffective.

The effect of collagen hydrolysate on the rate of collagen II synthesis by bovine chondrocytes was studied in an in vitro cell model. The culture medium was supplemented with collagen hydrolysate (CH) and the rate of collagen II biosynthesis by chondrocytes

Pronounced and long-lasting accumulation of oral collagen hydrolysate in the cartilage (Oesser S et al., 1999)



Marked or partial improvement of osteoarthritis problems during 16 weeks of treatment with collagen hydrolysate (Arquer Porcell A, 1996)



was compared with those cultured with native collagen I and II or a collagen-free protein hydrolysate. Collagen II was determined quantitatively after 48 hours of incubation by ELISA and by means of the rate of ^{14}C-proline incorporation in the extracellular matrix. While CH caused a dose-dependent increase in collagen II secretion by chondrocytes, native collagen and a collagen-free hydrolysate from wheat proteins exhibited no effect.

Oesser S, Seifert J. Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen, Cell Tissue Res 2003; 311 (3): 393–399.

Documented in animal studies with labeled substance: collagen hydrolysate is absorbed and then accumulates in cartilage tissue.

Collagen hydrolysate containing peptides with a molecular weight of 2.5 to 15 kDalton was ^{14}C-labeled and administered by gastric tube to mice, while the animals in a control group received ^{14}C-labeled proline. The radioactivity in the animals' plasma and tissues was determined over a period of 192 hours. During the first 12 hours after administration, 95 % of the collagen hydrolysate was absorbed. Labeled collagen hydrolysate and proline were found in comparable concentrations in all tissues except for cartilage tissue, where a particularly high and sustained accumulation of collagen hydrolysate was found. The radioactivity was twice as high as in the control group. These results confirm the intestinal absorption of collagen hydrolysate and its accumulation in cartilage tissue.

Oesser S et al. Oral administration of ^{14}C labeled gelatine hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL), J Nutr 1999; 129 (10): 1891–1895.

Ultrasound examinations show: collagen hydrolysate protects joint cartilage of active athletes.

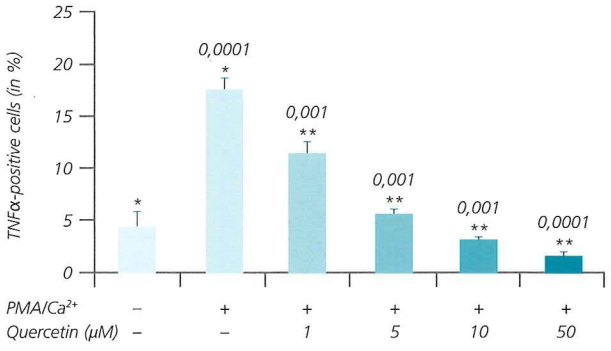
The effect of a collagen-containing diet on the layer thickness of joint cartilage in compartments of the humeral head and femoral condyles was studied by ultrasound using a standardised procedure in a total of 26 healthy active athletes. Some of the study participants received 10 grams of collagen hydrolysate daily over a period of six months, supplemented with magnesium and B-group vitamins, while the rest remained untreated. In the treated subjects a mean increase in cartilage layer thickness of 14 % was measured, while a decrease in layer thickness of 16 and 13 % was found in the control group in shoulder joint compartments.

Ribas Fernandez J Ll, Molinero Perez O. Efecto de los hidrolizados de gelatina en la prevención de las lesiones en deportistas. Archivos de Medicina del Deporte 1998; XV (66): 277–282.

Collagen hydrolysate reduces osteoarthritis pain in elderly patients and promotes joint mobility.

The effect of a collagen-containing diet on osteoarthritis-related joint pain and joint stiffness was studied in a total of 20 patients aged 50 to 70 years. The presence of osteoarthritis was confirmed by X-ray. Study participants received 10 grams of hydrolysed gelatine daily over a period of four months, supplemented with magnesium and B-group vitamins. An ordinal scale according to Keele was used for the self-rating of pain symptoms (pain on movement) by the patient and the patient also assessed joint mobility

Dose-dependent depression of TNFα in PMB cells by quercetin (Nair MP et al., 2006)



and general efficacy. 84.2 % of patients reported an improvement in the joint pain present before the start of treatment. Treatment was well tolerated without exception. No side effects were recorded.

Arquer Porcell A, Pujol Amat P. Ejercicio físico en la Tercera Edad, Revista Española de Medicina de la Educación Física y el Deporte 1996; 5 (3): 121–128.

3 Protective effects of vitamin C

The Framingham study shows: anti-oxidative micronutrients protect against the development and progression of knee osteoarthritis.

ROS-induced tissue damage results in various degenerative manifestations during the ageing process. The question was therefore raised as to whether the consumption of anti-oxidative micronutrients might be associated with a lower incidence of osteoarthritis (OA). Radiological findings of knee joints of participants in the Framingham study were recorded over several years and their dietary habits documented using a standardised questionnaire. Patients with knees without OA at the beginning of the study but who developed OA in the course of the study and those who had OA at the very beginning which then deteriorated in the course of the study were asked about their vitamin consumption. Using appropriate statistical procedures, the extent to which anti-oxidative substances, specifically vitamin C, β-carotene and vitamin E, or conversely non-anti-oxidative substances, such as vitamin B1, B6, Niacin and folic acid, were associated with OA progression was studied. Complete findings were obtained for 640 study participants. OA of the knee had developed in 81 knees and deteriorated in 68 knees compared to the preliminary findings. A threefold reduced risk of progression of OA and in particular of protection of the joint cartilage was found in study participants taking vitamin C, while high-dose intake of vitamin C primarily protected against the development of joint pain. These effects were not demonstrated with non-anti-oxidative micronutrients. The intake of high dose anti-oxidative micronutrients, and particularly of vitamin C, can accordingly reduce the risk of OA progression.

McAlindon TE et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? Arthritis Rheum 1996; 39 (4): 648–656.

4 Protective effects of quercetin

Quercetin inhibits COX-2 and other inflammation markers.

In cultures of human Chang liver cells, quercetin causes a dose-dependent inhibition of the markers present in the inflammatory process, iNOS, COX-2 and CRP, very probably by blockade of NF-κB activation. COX-2 plays an essential role in the pathobiochemistry and pharmacotherapy of osteoarthritis. Because of its inhibitor effects on COX-2, quercetin might be described as a plant COX-2 inhibitor.

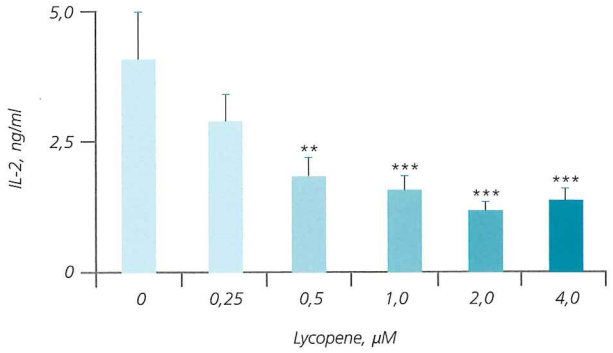
Garcia-Mediavilla V et al. The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells. Eur J Pharmacol 2007; 557 (2–3): 221–229.

Quercetin has an anti-inflammatory effect because it inhibits the production of tumour necrosis factor alpha (TNF-α).

Flavonoids are widely found in plant nutrients. These anti-oxidants can exert considerable anti-allergic and anti-inflammatory effects. Quercetin is a flavonoid that is safe to use. The mechanism of its anti-inflammatory effect was studied by determining the production and gene expression of the pro-inflammatory cytokine TNF-α in human peripheral blood mononuclear cells. In this model quercetin caused significant, dose-dependent inhibition of TNF-α gene expression and production.

Nair MP et al. The Flavonoid Quercetin Inhibits Pro-inflammatory Cytokine (Tumor Necrosis Factor Alpha) Gene Expression in Normal Peripheral Blood Mononuclear Cells via Modulation of the NF-κB-System. Clinical and Vaccine Immunology 2006; Mar: 319–328.

Dose-dependent inhibition of IL-2 in PMB cells by lycopene (Bessler H et al., 2008)



5 Protective effects of lycopene

Lycopene inhibits the formation of certain cytokines by blood mononuclear cells.

Regular consumption of tomato products is said to have beneficial immunomodulatory effects. In vitro studies have also shown that tomato extract has anti-oxidative, anticarcinogenic and antithrombotic properties. As tomatoes have a high content of carotinoids and particularly lycopene, the in vitro effects of lycopene were studied on peripheral blood mononuclear cells from healthy subjects. Lycopene caused a dose-dependent inhibition of IL-2, IL-10 and IFNγ release. This immunomodulatory effect recommends the use of lycopene as a food supplement for the prevention of certain diseases.

Bessler H et al. In vitro effect of lycopene on cytokine production by human peripheral blood mononuclear cells, Immunol Invest 2008; 37 (3): 183–190.

Lycopene is safe at a daily dose of 5 mg in adults.

This conclusion was reached by official expert committees in the Netherlands considering two applications on this subject. The corresponding reports (Lycopene, second opinion regarding consumer safety, in accordance with European Regulation 258/97 concerning novel foods and novel ingredients 2004 and Tomato extract with lycopene, Assessment of safety for the consumer, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients 2008) can be seen under *www.novel-foods.nl*.

Patient information

ARTILANE®

Liquid formulation
15 single dose drinking vials
On the basis of hyaluronic acid and antioxidants

Food supplement based on highly purified, enzymatically hydrolysed collagen (Colatech®) and hyaluronic acid, tomato concentrate containing 2 % lycopene *(Solanum lycopersicum)*, vitamin C and quercetin.

Ingredients: water, fructose (sweetener), highly purified, enzymatically hydrolysed collagen (Colatech®), modified starch (thickener), citric acid (acidity regulator), sodium chloride (flavour enhancer), potassium sorbate (preservative), tomato concentrate containing 2 % lycopene (*Solanum lycopersicum*), vitamin C, quercetin, colloidal silicone dioxide (anti-caking agent), hyaluronic acid, raspberry flavour and cellulase.

Instructions for use: drink the contents of one vial daily, either directly from the vial or diluted in half a glass of water.

Nutritional information (average per 100 g): protein: 19.6 g; carbohydrate: 32.8 g (of which sugar: 29.4 g); fats: < 0.5 g.

Energetic value: 100 g provide approx. 214.1 kcal (896.2 kJ); 1 ampoule provides approx. 75.1 kcal (314.3 kJ).

One vial contains 7 g highly purified, enzymatically hydrolysed collagen (Colatech®), 25 mg hyaluronic acid, 75 mg tomato concentrate containing 2 % lycopene, 30 mg quercetin and vitamin C.

Vitamins	Per 100 g	Per vial	% RDD*/ampoule
Vitamin C	171 mg	60 mg	100 %

* RDD = Recommended daily dose

SHAKE BEFORE USE.

Since this is a natural product it may change colour, smell and taste without affecting the quality of the product.

Do not exceed the recommended daily dose.
Do not use as a substitute for a balanced diet and a healthy lifestyle.
Keep the product out of the reach of children.
Store at room temperature, below 25 °C.

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