

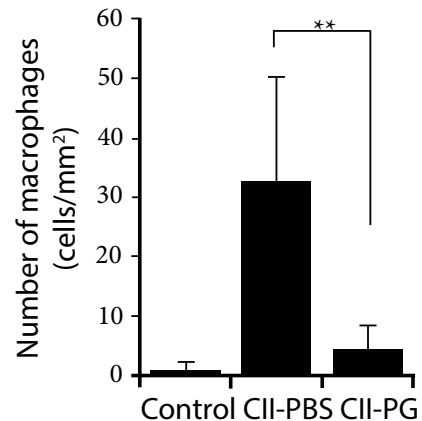
Proteoglycans (PGs) can be found in connective tissues such as skin, bone, and cartilage, where they form a complex with collagen, fibronectin, laminin, hyaluronic acid, and other glycoproteins. The basic chemical structure of PGs is a complex glycohydate composed of a core protein covalently bonded with one or more glycosaminoglycan side chains. Juvecol® is the proteoglycans extracted from salmon cartilage. Proteoglycans from salmon cartilage have been commonly consumed as a traditional food in Japan for many years (Takahashi, 2015). A tremendous amount of work has been done over the past several decades to understand the role and mechanisms of action for proteoglycan.

Accumulating research evidence has already shown that proteoglycans extracted from salmon cartilage have immunomodulatory effects, including suppressing inflammatory responses of macrophages induced by stimulation with heat-killed bacteria and attenuating induced colitis in a mouse model as well as experimental autoimmune encephalomyelitis (EAE) through daily oral administration (Yoshimura, 2014). Our partner, Ichimaru Pharcos has developed a high quality and purified proteoglycan using salmon cartilage caught in specific areas in Japan (Hokkaido and Aomori).

## Joint Health

The immunomodulatory effect of salmon proteoglycans PG (sPG) on the progression of arthritis was investigated in a mouse model. In this research, mice with collagen-induced arthritis (CIA) were administered sPG powder dissolved in phosphate-buffered saline at a concentration of 10 mg/mL, with a dosage of 2 mg of PG per os daily. The results showed that the percent incidence and clinical scores of CIA in the sPG-administered mice decreased significantly in comparison with the control group. From day 45 after the first immunization, the average clinical scores of CIA in the sPG-administered group differed significantly from those of the control group ( $p < 0.05$ ). In addition, histological analysis of ankle joints showed that synovitis and osteoclastic bone resorption were attenuated by daily oral administration of sPG (Yoshimura, 2014). Immunostaining showed that the infiltration of macrophages and neutrophils and accumulation of the osteoclasts decreased in the joints of PG-administered mice, suggesting the role of sPG in suppressing the infiltration of inflammatory cells and accumulation of osteoclasts in the joints (Figure 1). In addition, sPG-administered mice showed decreased local expression of various inflammatory cytokines, including interleukin (IL)-17A, IL-6, IL-1 $\beta$ , IFN- $\gamma$ , etc. (Yoshimura, 2014)

**Figure 1. Administration of sPG attenuated infiltration of macrophages and neutrophils, as well as the accumulation of osteoclasts**



Human articulation consists of cartilage cells, cartilage matrix, subchondral bone, tendons, and ligaments around the articulation and muscles. These components undergo various changes as our bodies age. Among these changes, the change of cartilage matrix is the key factor for developing osteoarthritis, which is thought to be related to the fact that the turnover period for the protein of this collagen and proteoglycan is relatively longer for older people. In a randomized, placebo-controlled, double-blind clinical study with 31 healthy subjects between ages 40 and 69, both pain VAS, right and left knee extension, and flexion showed significant differences in the intragroup (sPG versus control) comparison ( $p < 0.05$ ) and in the intergroup (sPG group) comparison of changes from the base line ( $p < 0.05$ ) (Najima, 2016).

## Skin Health

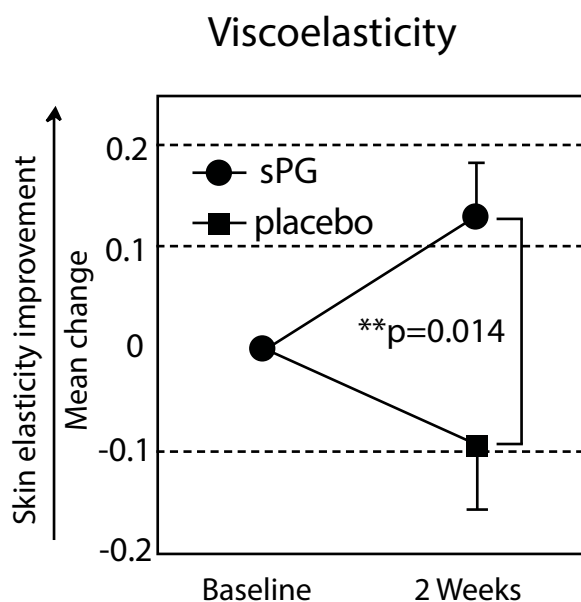
As we know, the skin is the largest organ of the human body, and it plays many important roles in regulating body temperature, water & lipid stores, and mitigation of environmental stresses including UV exposure, heat, injury, and infections (Proksch, 2008). Reduced skin function has been observed in aged skin; this includes some chronic skin diseases, which may be caused by decreasing collagen and lipid content, loss of fibroblasts, change of hormone levels, less supplementation of nutrition, and various other factors (Takahashi, 2015). A randomized, double-blind, placebo-controlled human clinical study conducted in 19 healthy subjects evaluated the effect of sPG ingestion on skin condition. This study showed that sPG ingestion is able to improve skin condition, especially skin elasticity (Figure 2). In this study, the researchers found that ingestion of a 5-mg sPG capsule daily for

# Juvecol® Overview

NEXTY Award winning proprietary salmon cartilage extract for joint health and skin beauty

2 weeks showed a significant improvement in skin viscoelasticity, recovery, and skin looseness when compared with the placebo group ( $p < 0.05$ ). Also, the number of under-eye wrinkles was significantly reduced in the sPG group after ingestion compared with the placebo group ( $p < 0.05$ ). In addition, the numbers of conspicuous pores and darkened pores were also significantly reduced from base line after sPG ingestion ( $p = 0.045$  and  $p = 0.035$ , respectively). Last but not least, the number of blotches was significantly decreased from base line after sPG ingestion ( $p = 0.045$ ) compared with no significant change in the placebo group ( $p = 0.573$ ). This trial also evaluated skin moisture. The researchers found that ingestion of sPG could slightly improve skin moisture as well (Takahashi, 2015). All these outcomes from this clinical study strongly support that ingestion of sPG could bring improvement of rough skin during the aging process.

**Figure 2. Administration of sPG showing significant improvement in human skin elasticity over 2 weeks**



## Immune Modulation

Many of sPG's functions are thought to be related to its immune-modulating properties. In an induced experimental autoimmune encephalomyelitis (EAE) mouse model, daily oral administration of sPG attenuated clinical and histological severity of EAE in a dose-dependent manner. Administration of sPG suppressed interferon- $\beta$  production and CCL2 expression in the spinal cord that is the inflamed site of EAE. Ex vivo experimentation showed that administration of PG suppressed IFN- $\gamma$  and IL-17 production from lymphocytes from draining lymph nodes in response to

MOG restimulation. In addition, administration of sPG suppressed the expression of IL-6, IL-21, IL-23 receptor, and retinoic acid-related orphan receptor  $\gamma$ t and enhanced the expression of Foxp3 in both draining lymph nodes and spinal cords (Sashinami, 2012).

## Conclusion

Salmon nasal cartilage has been traditionally consumed in Japan to maintain joint health as well as for its beneficial effects on overall health. Many safety studies have shown no adverse effects (Takahashi, 2015). sPG is considered a safe and promising prophylactic agent based on the tremendous amount of published scientific research over the past several decades. sPG is thought to function through its immune-modulating ability. Many clinical studies have already shown that continuous consumption of sPG from salmon is beneficial in the improvement of arthritis; attenuating knee discomfort; improving skin conditions associated with aging, UV exposure, and chronic infections; and ultimately in improving people's quality of life.

## References

- Buckwalter & Rosenberg. "Electron Microscopic Studies of Cartilage Proteoglycans." *Journal of Biological Chemistry* 257(16) (1982):9830-9839.
- Har-El & Tanzer. "Extracellular Matrix 3: Evolution of the Extracellular Matrix in Invertebrates." *The FASEB Journal* 7(2) (1993):1115-1123.
- Hook et al. "Cell-Surface Glycosaminoglycans." *Annual Review of Biochemistry* 53 (1983):847-869.
- Najima et al. "Usefulness of the Supplement Containing Proteoglycan for Japanese Healthy People Feeling Knee Discomfort." *Medical Consultation and New Remedies*. 53(3) (2016): 228-235.
- Proksch et al. "The Skin: An Indispensable Barrier." *Exp. Dermatol* 17 (2008):1063-1072.
- Sashinami et al. "Salmon Proteoglycan Suppresses Progression of Mouse Experimental Autoimmune Encephalo myelitis via Regulation of Th17 and Foxp3(+) Regulatory T Cells." *Life Sci* 17(91)(2012):25-26.
- Takahashi et al. "Ingestion of Salmon Nasal Cartilage-Derived Proteoglycan Improves Skin Condition: A Randomized, Double-Blind, Controlled Study." *Immune. Endoc. & Metab, Agents in Med. Chem* 15 (2015):160-167.
- Takahashi et al. "Safety Evaluation of Industrially Extracted, Highly Purified Proteoglycan from Salmon Nasal Cartilage." *Pharmacometrics* 89(1/2) (2015):15-22.
- Yoshimura et al. "Attenuation of Collagen-Induced Arthritis in Mice by Salmon Proteoglycan." *Biomed Research International*