

# Beneficial Effects of Collagen Hydrolysate: A Review on Recent Developments

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## Abstract

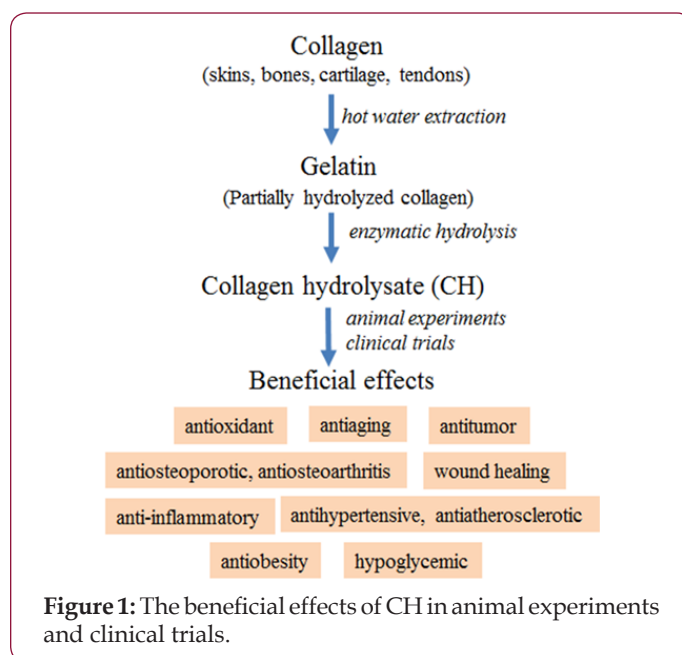
Collagen hydrolysate (CH) has received increasing attention in recent decades. This review mainly summarizes the recent developments (year 2010-2017) regarding the beneficial effects of CH in animal experiments and clinical trials. These beneficial effects include antioxidant, anti aging, anti osteoporotic and anti osteoarthritis, anti-inflammatory, anti tumor, wound healing, anti hypertensive and anti atherosclerotic, anti obesity and hypoglycemic effects. We also make comments on the current researches and give suggestions for future studies in this review. Considering the wide availability of CH in the field of pharmaceuticals and foods, the study of the potential beneficial effects of CH provides guidance to develop CH-based health care supplements for disease prevention and/or treatment.

**Keywords:** Collagen Hydrolysate; Beneficial Effect; Animal Experiment; Clinical Trial

## Introduction

Collagen is the main structural protein of the different connective tissues, such as skin, bone, cartilage and tendons, and comprises about one-third of total proteins in mammals. Collagen extracted from collagen-rich materials with hot water is known as gelatin. The common materials used for extracting gelatin include pig skin (46%), bovine hide (29.4%), bones (23.1%) and other sources (1.5%) [1]. However, fish gelatin has received great attention in recent years due to the religions, cultures and health concerns. The further enzymatic hydrolysis of gelatin results in collagen hydrolysate (CH). CH has long been used in pharmaceuticals and foods in many countries and regions, such as United States, Europe, China and Japan. Approved as Generally Recognized As Safe (GRAS), the safety of CH has been affirmed by the Food and Drug Administration (FDA) Center for Food Safety and Nutrition. The bioavailability and absorption of CH have also been widely studied. It has been reported that CH is more easily absorbed and has higher bioavailability than gelatin [2,3]. Besides free amino acids, small peptides especially dipeptide and tripeptide are also absorbed into body by peptide transporter 1 (PepT1) [4]. To date, more than 30 peptides (mainly dipeptides and tripeptides) have been identified in blood after gelatin and CH intake, and Pro-Hyp is the most abundant collagen-derived peptide [5-7]. These peptides may exert various beneficial effects on body health as previous

studies reported [8-9]. In this paper, we will mainly focus on the recent findings (year 2010-2017) regarding the beneficial effects of CH in animal experiments and clinical trials (Figure 1). The possible mechanisms underlying CH will also be briefly discussed.



**Figure 1:** The beneficial effects of CH in animal experiments and clinical trials.

## **Beneficial Effects**

### **Enhancing Antioxidant Capacity**

CH itself has good antioxidant activity as demonstrated by *in vitro* assays [10,11]. CH intake also increases the activities of antioxidant enzymes in body, including SOD, GSH-Px and CAT [3,12]. Nuclear factor E2-related factor 2 (Nrf2)-antioxidant response element (ARE) pathway plays a central role in regulating antioxidant enzymes. Therefore, we speculate that CH exerts its antioxidant effect in a direct and/or indirect manner. More work is needed to investigate the effect of CH on Nrf2-ARE signaling.

### **Anti aging effect**

Anti aging effect of CH has been widely investigated in several animal models, including photo aged model, chronologically aged model and acetone-induced dry skin model [3,12-15]. General beneficial effects, including increasing skin hydration, decreasing the formation of deep wrinkles and improving skin elasticity, are also observed in clinical trials after taking 10g of CH once a day for more than 6 weeks [16]. It should be noted that anti aging effect of CH is more obvious on women aged more than 30 years. Mechanisms underlying the beneficial effects may be involved in the dual effects of CH on skin collagen synthesis and degradation, as previous study reported [13].

### **Preventing and treating osteoporosis and osteoarthritis**

Anti osteoporotic and anti osteoarthritis effects of CH have been reviewed by Daneault et al. [17] and Porfirio et al. [18]. Daily doses equivalent to 12g of CH significantly promotes an improvement in the symptoms of osteoarthritis and osteoporosis [18]. Combined CH with other nutritional ingredients has received much interest. It has been reported that combined oral administration of CH with calcium and vitamin D has better effects on bone health than alone administration of CH or calcium and vitamin D [19-21]. Future studies are needed to determine the optimal form and optimal dose of CH.

### **Enhancing wound healing**

Oral administration of marine CH is reported to enhance cutaneous wound healing and angiogenesis in rats [22-23]. In addition to elevated VEGF and FGF-2 expression, the effect of CH on fibroblast may be one of the mechanisms underlying enhanced wound healing, as previous study reported that Pro-Hyp, a collagen-derived dipeptide, exerts a chemotactic action on fibroblast and stimulates fibroblast proliferation [8].

### **Anti-inflammatory effect**

Glycine is one of the major structural units of collagen, accounting for one-third of the amino acids. CH has the ability to reduce inflammatory responses [24,25]. This effect may be constituted by inhibiting the production of pro-inflammatory cytokine via glycine-gated chloride channels (GlyR).

### **Antitumor effect**

Liang et al. reported CH intake inhibited spontaneous tumor incidence and increase life span in Sprague-Dawley (SD) rats [26]. Our previous study found that CH intake inhibited platelet

release and down regulated proangiogenic factors in blood [27]. Considering angiogenesis is of key importance in the process of tumor progression. Our results provide a possible mechanism underlying antitumor effect of CH.

### **Reducing the risk of cardiovascular diseases**

Antihypertensive effect of CH has been reported in animal experiments and clinical trials [28,29]. Oral administration of collagen derived Gly-Leu-Pro significantly decreases systolic blood pressure by inhibiting angiotensin I converting enzyme (ACE) [28]. Tang et al. [30] found that oral administration of collagen tripeptide had an inhibitory effect on atherosclerosis development in hypercholesterolemia rabbits [30]. Platelets are involved in the pathophysiology of atherosclerosis and thrombosis. CH has an inhibitory activity on platelet release and platelet aggregation, which may justify potential application of CH as a health care supplement to prevent and/or treat atherosclerosis and thrombosis-related cardiovascular diseases [27].

### **Other effects**

CH intake has an effect on the absorption and metabolism of lipid and glucose. CH significantly reduces high fat diet-induced body weight gain and down regulates serum levels of total cholesterol, triglyceride and low-density lipoprotein [31]. Further, CH could alter lipid metabolism-related gene expression and the unfolded protein response in mouse liver [32]. The hypoglycemic effects of CH have also been reported [33,34]. It has been reported that CH can improve glucose tolerance by inhibiting intestinal glucose uptake and enhancing insulin secretion [34], suggesting the anti-diabetic property of CH.

## **Conclusion and Perspective**

Increasing evidence demonstrates that CH has various beneficial effects on body health. Those effects make CH new and potential healthcare supplement for disease prevention and/or treatment in pharmaceuticals and foods. However, several issues should be noted and need to be further explored. First, many *in vitro* studies only focus on the biological activities of CH, neglecting its tolerance in gastrointestinal tract. Certain collagen peptides isolated in *in vitro* studies may be hydrolyzed by gastrointestinal enzymes and exert no biological activity in body as expected in *in vitro* studies. *In vitro* simulated GI digestion and Caco-2 mono layers have been widely used and allow the prediction of oral compounds digestion and absorption in humans. Second, although many beneficial effects of CH have been reported, what is the peptide sequence responsible for certain beneficial effect? The study on structure-activity relationship will guide the application of CH. Third, the biological activities of protein hydrolysates are highly affected by their molecular structure and weight, which are greatly impacted by their processing conditions. Therefore, processing conditions are needed to be optimized for obtaining CH with certain beneficial effect.

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