**ZAMMEX COLLAGEN – CLAIMS SUBSTANTIATION**

June 27, 2019

Christopher Norton
Chief Executive Officer
Zammex Nutrition, LLC
2100 N. Broadway, Suite 205
Santa Ana, CA 92706

Dear Mr. Norton,

**Claims Substantiation – Zammex collagen products**

The following is a summary of the scientific and clinical research related to the ZAMMEX collagen product line its benefits in terms of human bioavailability.

- We performed a comprehensive review of the totality of evidence regarding ingredients from the ZAMMEX collagen products. These ingredients were evaluated for evidence of an effect on aging, antioxidant features, and eye health.
- From this comprehensive review, we have generated evidence tables aimed at representing each of the physiologic processes.
- From these tables, we have analyzed the totality of evidence and have created substantiated scientific statements that we believe represent an accurate summary of this evidence.
- Based on these statements, we have worked with the client to generate new claims that are based solely on the substantiated statements that summarize the totality of evidence from the evidence tables.

Ingredients reviewed in this substantiation document are specific to the ingredients selected by the sponsor that are found in the ZAMMEX collagen products and include the following:

- **Low molecular weight collagen**

These following evidence tables are based on the totality of the evidence. Each statement outlined below is supported by an evidence table, which is attached. We have graded each human study based on the following grading criteria:

- Class A Evidence: Randomized, controlled trials
- Class B Evidence: Non-randomized prospective studies, Cross-sectional studies, Open-label studies
- Class C Evidence: Retrospective studies
- Class E Evidence: Reviews, Expert Opinion, Guidelines
- Class M Evidence: Meta-analyses
- Class S Evidence: Systematic reviews
- Animal Study
- Laboratory / In-vitro Study

Should you have any additional questions, it would be my pleasure to answer them. I can be reached directly at email, mpakdaman@pakdamanconsulting.com, and phone number, (818) 233-0073.

Sincerely,

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**Current Claims** –The following table demonstrates claims that can be substantiated based on our research:

| Suggested Claim | Substantiated Statements & Evidence Tables |
|---|---|
| Low molecular weight substances, including collagen, have improved absorption and bioavailability. | • Clinical and laboratory data demonstrate that, all other properties being equal, lower molecular weight compounds generally have increased intestinal absorption and bioavailability (Evidence Table 1).<br>• Clinical studies demonstrate that collagen formulations with molecular weight below 3000 Daltons (Da) have superior intestinal absorption and bioavailability compared with higher molecular weight formulations (Evidence Table 3). |
| Water soluble formulations of various products, including possibly collagen, have improved absorption and bioavailability. | • Clinical and laboratory data demonstrate that, all other properties being equal, increased water solubility generally is linked to increased intestinal absorption and bioavailability (Evidence Table 2).<br>• Limited human and animal studies have shown that formulations of collagen with increased water solubility may be effective in supporting healthy feeling joints (Evidence Table 3). |
| ZAMMEX Collagen has lower molecular weight and superior water solubility compared with competitors, indicating superior bioavailability and intestinal absorption. | • The ZAMMEX collagen peptide formulation demonstrates significantly lower molecular weight compared to two other popular collagen peptide formulations (Evidence Table 3).<br>• The ZAMMEX collagen peptide formulation was shown in a video demonstration to dissolve more quickly in water compared with a popular competitor (Evidence Table 3).<br>• Clinical and laboratory data demonstrate that, all other properties being equal, lower molecular weight compounds generally have increased intestinal absorption and bioavailability (Evidence Table 1).<br>• Clinical studies demonstrate that collagen formulations with molecular weight below 3000 Daltons (Da) have superior intestinal absorption and bioavailability compared with higher molecular weight formulations (Evidence Table 3).Clinical and laboratory data demonstrate that, all other properties being equal, increased water solubility generally is linked to increased intestinal absorption and bioavailability (Evidence Table 2).<br>• Limited human and animal studies have shown that formulations of collagen with increased water solubility may be effective in supporting healthy feeling joints (Evidence Table 3). |

## *Summary of **Substantiated** Scientific Statements*

**1)** Clinical and laboratory data demonstrate that, all other properties being equal, lower molecular weight compounds generally have increased intestinal absorption and bioavailability (Evidence Table 1).

A. Two (2) Grade-B studies, comprising a total of 32 healthy volunteers, demonstrate increased intestinal absorption with lower molecular weight compounds of chondroitin of antipyrine, atenolol and enalaprilat (Lennernas, Ahrenstedt, and Ungell 1994; Volpi et al. 2019).

B. One (1) animal study on rabbits revealing increased bioavailability of enoxaparin (low molecular weight heparin) after oral administration. Lower molecular weight formulations were found to have increased bioavailability (Scala-Bertola et al. 2009).

C. Multiple in-vitro studies involving lower molecular weight preparations of phenolic acids, soluble microbial products, and various peptides have increased intestinal absorption and cellular uptake (Sumaila et al. 2019; Veber et al. 2002; Wang and Li 2017; Wu et al. 2014; Wu, Liu, and Liang 2019; Zhang et al. 2018).

D. One (1) review article demonstrating decreased molecular weight of ingested particles results in increased release of drug into bloodstream (Jao et al. 2017).

E. One (1) review article summarizes multiple studies that demonstrated improved absorption of low molecular-weight heparin (Akhtar et al. 2018).

**2)** Clinical and laboratory data demonstrate that, all other properties being equal, increased water solubility generally is linked to increased intestinal absorption and bioavailability (Evidence Table 2).

A. Five (5) Grade-A studies, comprising a total of 59 healthy volunteers found that water-soluble formulations of polyethylene glycol, fenofibrate, multivitamin combinations, dipyridamole, and propofol had superior bioavailability compared with less water-soluble formulations (Basit et al. 2001; Bukara et al. 2016; Johnson et al. 2014; Ricevuti et al. 1991; Wozniak et al. 2015).

B. One (1) Grade-A study comprising of 8 patients with malabsorption from cystic fibrosis found that a water-soluble vitamin E formulation (Aqua-E) was superior to an oil-based softgel formulation with regard to absorption of γ -tocopherol (Papas, Kalbfleisch, and Mohon 2007).

C. Six (6) Grade-B studies, comprising a total of 66 healthy volunteers found increased bioavailability linked to water-soluble forms of avizafone, magnesium, cucumin, lornoxicam, alpha-tocopherol, and coenzyme q10 (Abbara et al. 2009; Dogterom et al.

2018; Kanai et al. 2012; Moutasim, ElMeshad, and El-Nabarawi 2017; Thakker et al. 1987; Zmitek et al. 2008).

D. One (1) Grade-B study, comprising 26 liver transplant patients, demonstrates that a water-soluble vitamin E preparation combined with cyclosporine resulted in improved cyclosporin absorption (Pan et al. 1996).

E. Three (3) review articles of in-vitro studies demonstrated that increased water solubility of supercritical fluid (SCF)-assisted particles and amorphous agomelatine is linked to increased oral absorption and bioavailability (Abuzar et al. 2018; Barmpalexis et al. 2018; Lipinski 2000).

3) Clinical studies demonstrate that collagen formulations with molecular weight below 3000 Daltons (Da) have superior intestinal absorption and bioavailability compared with higher molecular weight formulations (Evidence Table 3).

A. One (1) Grade-A study of 80 patients with progressive hip or knee osteoarthritis found that a formulation of collagen with molecular weight 1500 to 2500 Da resulted in significant reduction in pain and other subjective markers when compared with placebo (Schauss et al. 2012).

B. One (1) Grade-A study of 200 diabetic patients and 50 normal controls found improved markers of vascular injury with low molecular-weight formulations of collagen peptide when compared with placebo (Zhu et al. 2010).

C. One (1) Grade-B study of 4 healthy male volunteers found that collagen preparations with molecular weight 300 and 600 Daltons demonstrated more rapid accumulation in the blood compared to a collagen preparation with molecular weight 5000 Daltons (Yamamoto et al. 2016).

D. Five (5) animal studies of hydrolyzed collagen demonstrated improved intestinal absorption following oral administration of lower molecular weight collagen peptides (Sontakke et al. 2016; Taga et al. 2017; Wang et al. 2015; Watanabe-Kamiyama et al. 2010; Yamamoto et al. 2015).

E. Three (3) in-vitro studies of hydrolyzed collagen demonstrate that low molecular weight compounds below 5000 Da have superior bioavailability and transport efficiency (Benadiba, Serruya, and Maor 2018; Feng and Betti 2017; Nikolaeva et al. 2018).

4) Limited human and animal studies have shown that formulations of collagen with increased water solubility may be effective in supporting healthy feeling joints (Evidence Table 3).

A. One (1) Grade-B study of water-soluble, undenatured type II collagen (NEXT-II) found efficacy in improving pain in healthy volunteers with normal to little knee joint pain (Yoshinari et al. 2015).

B. One (1) animal study of water-soluble, undenatured type II collagen (NEXT-II) found efficacy in improving pain in arthritic mice and dogs (Yoshinari, Moriyama, and Shiojima 2015).

5) The ZAMMEX collagen peptide formulation demonstrates significantly lower molecular weight compared to two other popular collagen peptide formulations (Evidence Table 3).

   A. One (1) unpublished study demonstrates that 35.36% of the ZAMMEX collagen has molecular weight below 340 Da, 69.33% below 1250 Da, and 94.13% below 1500 Da. Data for competitor A was 23.77%, 45.73%, and 70.52%. Data for competitor B was 24.73%, 44.06%, and 66.98% (ZAMMEX).

6) The ZAMMEX collagen peptide formulation was shown in a video demonstration to dissolve more quickly in water compared with a popular competitor (Evidence Table 3).

   A. An unpublished video demonstration revealed complete dissolution of the ZAMMEX product in water in 7 seconds, compared with 25 seconds for the competitor. Of note, the competitor product also had increased precipitate (ZAMMEX).

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**Evidence Table 1**

Clinical and laboratory data demonstrate that, all other properties being equal, lower molecular weight compounds generally have increased intestinal absorption and bioavailability

| Study | Design | Sample Size | Study Population | Intervention / Product(s) | Dosage of Product(s) | Endpoint Measured | Result | Evidence Level |
|---|---|---|---|---|---|---|---|---|
| **Scala-Bertola 2009 (PMID: 19446753)** | Animal study | N / A | Rabbits | Enoxaparin granules<br>Bemiparin granules | N / A | Bioavailability | bioavailabilities for enoxaparin granules (0.45+/-0.12IU/mL; 19.00+/-0.30%, respectively) and for bemiparin granules (0.54+/-0.08IU/mL; 29.02+/-4.12%, respectively) were found after oral administration of granules loaded with ERS alone at a dose of 600IU anti-Xa/kg to rabbits. Lower molecular weight formulations of LMHW were found to have increased bioavailability in this animal study | Animal Study |
| **Lennernas 1994 (PMID: 7917779)** | Open-label study | n = 8 | Healthy volunteers | antipyrine, atenolol and enalaprilat injected through jejunal tube | Minimal doses | Net water flux<br>Intestinal absorption | Defines effective intestinal permeability as the ability of the intestinal mucosa to allow molecules of low molecular weight to absorb by passive diffusion.<br>permeability decreases markedly at molecular weight above 400 g/mol<br>Study noted significant net water absorption in parallel with an increased permeability of the two drugs with lowest molecular weight | B - Open Label Study |
| **Volpi 2019 (PMID: 30040242)** | Single-center, single-dose, open-label, randomized, 2-way, crossover study | n = 24 | Healthy volunteers | Chndroitin<br>molecular weight = 5120<br>dispersity = 2.2656 | 2400 mg | Blood samples for pharmacokinetic analysis | Lower molecular weight chondroitin demonstrated better absorption, better concentration for more prolonged periods of time in plasma, and an increase in charge density, along with a specific 6-sulfation of endogenous plasma CS. More pronounced chondroprotective effects were also noted. | B - Open Label Study |
| **Akhtar 2018 (PMID: 30021958)** | Review | N / A | Patients in need of anticoagulation | Low molecular weight heparin<br>Unfractionated heparin<br>Heparin sulfate | N / A | N / A | Low MW heparin is made via enzymatic depolymerization. The type of preparation of low MW heparin determines its mechanism. | E - Review |
| **Jao 2017 (PMID: 28772877)** | Review | N / A | N / A | N / A | N / A | Delayed drug release and bioavailability | Multiple studies show that decreased molecular weight results in increased release of drug into bloodstream.<br>Particle size is also important, as smaller particles can penetrate physiological barriers and affect release efficiency. Additionally, nanoparticles can induce magnetic properties that can affect drug delivery. | E - Review |
| **Sumaila 2019 (PMID: 30746572)** | In-vitro study | N / A | N / A | lipopolysaccharide polyelectrolyte complex encapsulated with rifampicin as the model drug | N / A | Absorption profile | Lower molecular weight particles resulted in increased encapsulationefficiency | In Vitro Study |
| **Veber 2002 (PMID: 12036371)** | In-vitro study | N / A | N / A | N / A | N / A | Oral bioavailability and molecular weight | higher oral bioavailability is associated with lower molecular weight, lower rotatable bond counts, lower hydrogen bond counts, and lower polar surface area. | In Vitro Study |
| **Wang 2017 (PMID: 27719884)** | In-vitro study | N / A | N / A | N / A | N / A | Bioavailability | PepT1, the peptide with lowest molecular weight, was involved in the transport of F3 (<500Da) and its bioavailability was highest among the compounds at 16.23%. | In Vitro Study |
| **Wu 2014 (PMID: 25379647)** | In-vitro study | N / A | human Caco-2 cell monolayer model | Three phenolic acids isolated from the flowers of Trollius chinensis Bunge: proglobeflowery acid (PA), globeflowery acid (GA) and trolloside (TS), | N / A | absorption properties, mechanism of action, and structure-property relationship | all three compounds were easily absorbed through passive diffusion, indicating high bioavailability | In Vitro Study |
| **Wu 2019 (PMID: 30878659)** | In-vitro study | N / A | aerobic microbia | Ultrafiltration (UF) fractionation was used to separate Soluble microbial products (SMPs) into homogenous components | N / A | bioavailability of individual molecular weight (MW) fractions of SMPs in surface water and the impact on by-products (DBPs) formation | Low molecular weight SMPs fractions (MW<10kDa) were major precursors for DBP and had the highest biotransformation | In Vitro Study |
| **Zhang 2018 (PMID: 29800739)** | In-vitro study | N / A | N / A | zinc ion (Zn(2+)) and exenatide complex functionalized nanoparticle (NP) oral delivery system<br>Low molecular weight protamine was used as a functional group to increase penetration of nanoparticles into the intestinal epithelium. | N / A | cell uptake and transmembrane transport markers | Nonparticles with low molecular weight protamine exhibited significantly improved penetration across the intestinal epithelium and increased bioavailability | In Vitro Study |

**Evidence Table 2**

Clinical and laboratory data demonstrate that, all other properties being equal, increased water solubility generally is linked to increased intestinal absorption and bioavailability

| Study | Design | Sample Size | Study Population | Intervention / Product(s) | Dosage of Product(s) | Endpoint Measured | Result | Evidence Level |
|---|---|---|---|---|---|---|---|---|
| **Basit 2001 (PMID: 11587486)** | Randomized, controlled trial | n=10 | Healthy adult male volunteers | 150 ml of orange juice (control)<br>150 mL orange juice with Polyethylene glycol (PEG) 400 (test). | Polyethylene glycol (10 g) | Position within gastrointestinal tract (measured by gamma camera) | Test group provides increased water solubility. The mean small intestinal liquid transit time = 236 min (control) vs. 153 min (test), representing 35% reduction in transit time. | A - Randomized Trial |
| **Bukara 2016 (PMID: 27648957)** | Randomized, controlled trial | n=12 | Healthy volunteers | Overnight fasting, followed by single dose of fenofibrate formulated with ordered mesoporous silica or a marketed product based on micronized fenofibrate. | Fenofibrate 33.5 mg | Plasma concentrations of fenofibric acid (fenofibrate metabolite) at up to 96h post-dose | The rate (Cmax/dose increased by 77%, tmax reduced by 0.75h) and extent of absorption (AUC0-24h/dose increased by 54%) of fenofibrate were significantly enhanced following administration of the ordered mesoporous silica based formulation, resulting in increased water solubility. | A - Randomized Trial |
| **Johnson 2014 (PMID: 25352732)** | randomized, controlled, crossover, interventional trial | n=15 | Healthy volunteers | single dose of either four tablets or two softgels at the full dose level, or one softgel at the half-dose level | β-carotene (28,640 IU), vitamin C (452 mg of ascorbic acid), vitamin E (400 IU provided as dl-α-tocopheryl acetate), zinc (69.6 mg as zinc oxide), and copper (1.6 mg as cupric oxide) | responses in bioabsorption: bioavailability of each micronutrient was based on the pharmacokinetic profiles established through 15 samplings for each ingredient/dosage form in plasma/serum over the course of one week | lipophilic nutrients β-carotene and vitamin E appear to have improved bioavailabilities when they are delivered from a readily water-soluble matrix | A - Randomized Trial |
| **Ricevuti 1991 (PMID: 1814737)** | randomized double blind cross over study | n=12 | Healthy volunteers | dipyridamole-beta-cyclodextrin complex (dip-beta-CD) vs. dipyridamole alone | Dipyridamole 25 mg and 75 mg | Blood dipyridamole levels | Dip-beta-CD showed better bioavailability than dipyridamole either after single or multiple doses. Dip-beta-CD had a greater AUC and Cmax, and a smaller Tmax (faster absorption). In addition, 100% of the subjects receiving a single dose of dip-beta-CD, as compared to 66.7% of those treated with dipyridamole, had plasma levels superior to 1 microgram/ml | A - Randomized Trial |
| **Wozniak 2015 (PMID: 26021605)** | double-blind, randomized, crossover, placebo-controlled, single ascending dose study | n=10 | Healthy volunteers | fospropofol (water-soluble propofol)<br>propofol | 400 mg | pharmacokinetic and pharmacodynamic parameters | Water soluble propofol (fospropofol) demonstrated systemic availability after oral consumption, likely due to water soluble properties | A - Randomized Trial |
| **Papas 2007 (PMID: 17216337)** | Randomized study | n=8 | Patients with malabsorption from cystic fibrosis | water-soluble vitamin E formulation (Aqua-E) vs. oil-based softgel formulation | 20 ml of Aqua-E or three oil-based softgels, which contained equivalent amounts of tocopherols | Blood tocopherol levels at 0, 2, 4, 8, 24, 48, and 168 hr | absorption of γ-tocopherol in Aqua-E was significantly greater than that of oil-based softgels. Study found that water-soluble formulation showed a marked and statistically significant increase in absorption of γ- tocopherol in malabsorbing patients with CF compared with an oil-based formulation. | A - Randomized Trial |
| **Abbara 2009 (PMID: 19681868)** | open, randomized, single-dose, three-way, cross-over study | n=20 | Healthy adult male volunteers | intramuscular injections of avizafone (water soluble diazepam), diazepam or avizafone combined with atropine and pralidoxime | avizafone (20 mg), diazepam (11.3 mg), atropine (2 mg), pralidoxime (350 mg) | Plasma concentrations of diazepam | The maximum concentration (Cmax)) of water soluble diazepam was higher than that obtained after injection of diazepam alone. Diazepam concentrations also reached their maximal value faster with the water-soluble compound | B - Open Label Study |
| **Dogteron 2018 (PMID: 29638147)** | Open Label Study | n=10 | Healthy volunteers | (a) single oral dose of 20 mEq magnesium L-lactate dehydrate under fasting conditions, (b) single intravenous (IV) infusion of 20 mEq magnesium sulfate, and (c) single oral dose of 20 mEq magnesium L-lactate dehydrate under fed conditions. | 20 mEq magnesium L-lactate dehydrate | Absolute bioavailability | Absolute bioavailabilities of the caplets under fasted and fed conditions, compared to IV magnesium sulfate, were 20.26% (fasted) and 12.49% (fed) in serum. The absorption and bioavailability is highly affected by the water solubility of the salt form. | B - Open Label Study |
| **Kanai 2012 (PMID: 21603867)** | Open Label Study | n=6 | Healthy volunteers | THERACUMIN (Water-soluble curcumin) | Curcumin 150 mg followed by 210 mg every 2 weeks | Plasma curcumin levels at 0,1,2,4,6, and 24h | THERACURMIN has improved water solubility with its mean particle size of 0.19 um, and oral administration of THERACURMIN demonstrated more than 30-fold higher bioavailability compared to that of conventional curcumin | B - Open Label Study |
| **Moutaim 2017 (PMID: 28283842)** | Open Label Study | n=4 | Healthy volunteers | Lornoxicam complexed with with β-cyclodextrin | Variable based on formulation | Drug plasma concentrations | Following administration of F2 and Zeficam(R), the respective maximum drug plasma concentrations (Cmax) were 510 and 532.5 ng/mL, at times (Tmax) of 1 and 2.5 h, of mean residence times (MRTs) of 12.25 and 11.35 h and of areas under the plasma curve [AUC(0-24)] of 5080.253 and 4815.775 ng/h/mL<br>Lornoxicam complexed with β-cyclodextrin has increased water solubility and increased bioavailability | B - Open Label Study |
| **Thakker 1987 (PMID: 3591727)** | Open Label Study | n=12 | Healthy volunteers | RRR-alpha-tocopherol (d-alpha-tocopherol), riboflavin, and pyridoxine hydrochloride | d-alpha-tocopherol (30 IU) riboflavin (15 mg) pyridoxine hydrochloride (5 mg) | Blood levels of RRR-alpha-tocopherol (d-alpha-tocopherol), riboflavin, and pyridoxine hydrochloride | Absorption of RRR-alpha-tocopherol was increased from the Aquabiosorb soft elastic gelatin (SEG) capsule formulation compared with the modified standard SEG capsule and the commercial tablet. . The enhanced bioavailability of vitamin E and the trend towards faster and more consistent absorption of riboflavin and vitamin B-6 from the SEG formulation may be related to the surfactant vehicle employed and the attendant wetting properties. | B - Open Label Study |
| **Zmitek 2008 (PMID: 18645245)** | Randomized three-period crossover clinical trial | n=14 | healthy non-smoking male volunteers | Q10Vital liquid<br>Q10Vital powder<br>Soft gel capsules with 30 mg of CoQ10 in soybean oil (control) | 30 mg CoQ10 | Bioavailability | Water solubility was increased significantly with the use of an inclusion complex with beta-cyclodextrin. Compared with non-water soluble formulation, statistically significant 120 and 79% increases over the reference were calculated for the Q10Vital liquid and powder, respectively | B - Open Label Study |
| **Pan 1996 (PMID: 8700793)** | Open Label Study | n=26 | Liver transplant patients (19 adults; 7 children) | Liqui-E, a water-soluble vitamin E preparation<br>Cyclosporin | Liqui-E 6.25 IU/kg | Cyclosporin whole blood concentration | With Liqui-E, the daily oral CyA requirements (mean ± SD) were decreased in adults from 22.6 ± 8.9 to 16.2 ± 7.3 mg/kg/day ($p<0.001$) and in children from 78.6 ± 34.1 to 53.7 ± 35.0 mg/kg/day ($p<0.02$). When given with Liqui-E, the daily cost of CyA decreased by 26% in both adults and children. Water solubility improved intestinal absorption and bioavailability | B - Open Label Study |
| **Abuzar 2018 (PMID: 29278733)** | Review of In-Vitro studies | N / A | N / A | supercritical fluid (SCF)-assisted particles | N / A | Water solubility | micronization, crystal morphology control, and formation of composite solid dispersion nanoparticles with polymers and/or surfactants allows for increased water solubility and thus increased bioavailability | E - Review |
| **Barmpalexis 2018 (PMID: 28989020)** | Review of In-Vitro and human studies | N / A | N / A | novel formulation of amorphous agomelatine (AGM) that exhibits enhanced in vitro dissolution rate | N / A | Bioavailability | In-vitro dissolution studies and clinical trials in healthy human volunteers showed a remarkable increase in the in vitro dissolution rate and a approximately 1.5-fold increase in bioavailability, respectively, compared to the marketed product. | E - Review |
| **Lipinski 2000 (PMID: 11274893)** | Review of In-Vitro studies | N / A | N / A | N / A | N / A | N / A | The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. The level of permeability or solubility needed for oral absorption is related to potency. Higher molecular weight is linked to higher lipophilicity, and, hence, poorer aqueous/water solubility | E - Review |

## Evidence Table 3

- Clinical studies demonstrate that collagen formulations with molecular weight below 3000 Daltons (Da) have superior intestinal absorption and bioavailability compared with higher molecular weight formulations.
- Limited human and animal studies have shown that formulations of collagen with increased water solubility may be effective in supporting healthy feeling joints.
- The ZAMMEX collagen peptide formulation demonstrates significantly lower molecular weight compared to two other popular collagen peptide formulations.
- The ZAMMEX collagen peptide formulation was shown in a video demonstration to dissolve more quickly in water compared with a popular competitor.

| Study | Design | Sample Size | Study Population | Intervention / Product(s) | Product Dosage | Endpoint Measured | Result | Evidence Level |
|---|---|---|---|---|---|---|---|---|
| **ZAMMEX** | **In-Vitro Study** | **N / A** | **N / A** | Hydrolyzed Collagen | N / A | N / A | Study found 35.36% of the ZAMMEX collagen has molecular weight below 340 Da, 69.33% below 1250 Da, and 94.13% below 1500 Da. Data for competitor A was: 23.77%, 45.73%, and 70.52%. Data for competitor B was: 24.73%, 44.06%, and 66.98%<br>Video demonstration revealed complete dissolution of the ZAMMEX product in water in 7 seconds, compared with 25 seconds for the competitor. Of note, the competitor product also had increased precipitate | In-Vitro Study |
| **Schauss 2012 (PMID: 22486722)** | Randomized controlled trial on OA-related symptoms | n=80 | Patients with physician-verified evidence of progressive osteoarthritis (OA) in their hip and/or knee joint. | BioCell Collagen (hydrolyzed chicken sternum) – MW 1500 – 2500 kDa vs. placebo<br>hydrolyzed collagen type II (300 mg)<br>depolymerized chondroitin sulfate (300 mg)<br>hyaluronic acid (50 mg). | Physician Global Assessment scores for joint pain<br>Visual analog scale (VAS) for pain | BCC group had significant reduction of VAS pain on day 70 ($p < 0.001$) and of WOMAC scores on days 35 ($p = 0.017$) and 70 ($p < 0.001$), as well as significant improvement in physical activities compared to the placebo group on days 35 ($p = 0.007$) and 70 ($p < 0.001$). | A - Randomized Trial |
| **Zhu 2010 (PMID: 20514986)** | Randomized controlled study | n=250 | type 2 diabetic patients with or without hypertension (n=200)<br>50 healthy subjects (n=50) | Marine collagen peptides (MCP)<br>MCPs-treated diabetics (n = 50)<br>placebo-treated diabetics (n = 50)<br>MCPs-treated diabetics with HTN (n=50)<br>placebo-treated diabetics with HTN (n = 50)<br>Healthy controls (n = 50). | N / A | markers of metabolic nuclear receptors: Free fatty acid, cytochrome P450, leptin, resistin, adiponectin, bradykinin, NO, and Prostacyclin | MCPs-treated patients showed marked improvementin markers of vascular injury compared with patients receiving placebo.<br>MCPs could offer protection against diabetes and hypertension by affecting levels of molecules involved in diabetic and hypertensive pathogenesis. | A - Randomized Trial |
| **Sontakke 2016 (PMID: 27573716)** | In-vitro and animal study | N / A | N / A | collagen tripeptide (CTP) prepared from fish scales & digested using collagenase from nonpathogenic Bacillus bacteria. | Not specified | Intestinal cell transport markers; plasma levels in rats | Low MW Hyp-containing peptides-GPH and PH-were better absorbed and reached higher plasma peptide (H-CP). | Animal study |
| **Taga 2017 (PMID: 28988478)** | In-vitro and animal study | N / A | Mice | ginger-degraded collagen hydrolysate Synthesized using 10 Kda molecular weight cut-off (MWCO) | N / A | Absorption and bioavailability | Oral administration experiments using mice revealed that cyclo(Ala-Hyp) and cyclo(Leu-Hyp) were absorbed into the blood at markedly higher efficiencies compared to collagenous oligopeptides, including Pro-Hyp. | Animal study |
| **Wang 2015 (PMID: 25410396)** | Animal study | N / A | Healthy female Sprague–Dawley rats | Collagen peptides with molecular weight cut-offs (MWCO) of 3000 Da | 4000 mg / kg | bioavailability of gelatin, pharmacokinetics | Gelatin had high oral bioavailability. Nearly half of digested gelatin was absorbed from the intestine in the form of various collagen peptides. | Animal study |
| **Watanabe-Kamiyama 2010 (PMID: 19957932)** | Animal study | N / A | Rats | LMW-CH (low MW collagen hydrolysate) – 800 Da; Prepared from chicken legs | 288 mg | Analysis of radiolabeled tracers | LMW-CH had improved bioavailability<br>Orally ingested collagen hydrolysate resulted in increased bone mineral density | Animal study |
| **Yamamoto 2015 (PMID: 26155906)** | Animal study | N / A | Rats | Collagen tripeptide processed by endopeptidase to decrease MW<br>Mean MW of short chain peptide = 300 Da | 446 mg/kg | analysis of isotopically labeled Gly-Pro-Hyp radioactive tracer in blood plasma by thin layer chromatography (TLC). | CTP was absorbed into the blood rapidly and thereafter also transported into the tissues rapidly because the mean molecular weight of CTP is much smaller than that of conventional collagen peptide and the digestion process of CTP is omitted in digestive tract. | Animal study |
| **Yoshinari 2015 (PMID: 25751538)** | Animal study | N / A | Mice with collagen-induced arthritis<br>Dogs with moderate arthritis | water-soluble, undenatured type II collagen (NEXT-II) vs. placebo | Undenatured type II collagen (10 mg) | Adverse event data. Physical health and serum chemistry | NEXT-II exhibited significant efficacy in ameliorating pain and inflammation in collagen-induced arthritis in mice<br>NEXT-II exhibited a significant reduction in overall pain in moderately arthritic dogs without changing physical parameters. | Animal study |
| **Yamamoto 2016 (PMID: 26934933)** | Open-Label Study | n=4 | Healthy male volunteers | tripeptide fraction of CTP (CTP-100) (MW 300)<br>CTP preparation containing ca. 50% Gly-X-Y tripeptides (CTP-50) (MW 600)<br>Collagen peptide that did not contain tripeptides (CP), (MW 5000) | 80 mg/kg | Pharmacokinetic absorption analysis | CTP-100 and CTP-50 (lower molecular weight collagens) demonstrated more rapid increase in blood collagen (concentration of Gly-Pro-Hyp), and reached Tmax in 30–60 min | B - Open Label Study |
| **Yoshinari 2015** | Open-Label Study | n=11 | Healthy volunteers in the borderline between normal and little knee joint pain | 12-week intervention<br>Water-soluble, undenatured type II collagen (NEXT-II) | 40 mg NEXT-II® (10 mg as undenatured type II collagen) | Visual analog scale (VAS) for knee pain<br>Western Ontario McMaster index (WOMAC) score for knee pain | NEXT-II® treatment significantly reduced WOMAC and VAS scores compared to subjects at baseline | B - Open Label Study |
| **Benadiba 2018 (PMID: 30272033)** | In-vitro study | N / A | N / A | Shore Magic(R) Hydrolyzed Collagen (SMC) | N / A | in vitro barrier models with translational significance | Transport studies on simulated gastrointestinal (GI) digestion | Lab study showed markers that suggest increased bioavailability of their "low molecular weight" product, but the specific weight in daltons is not mentioned. They only note that 5000 Da is "typical" of hydrolyzed collagen | In-Vitro Study |
| **Feng 2017 (PMID: 28159262)** | In-vitro study | N / A | N / A | Collagen extracted from raw bovine hide hydrolyzed by one of: Alcalase, Flavourzyme, or trypsin | N / A | Transport studies on simulated gastrointestinal (GI) digestion | Hydrolyzed collagen with lower MW profile showed greater resistance to GI digestion and greater transport efficiency than the unhydrolyzed collagen control. | In-Vitro Study |
| **Nikolaeva 2018 (PMID: 30225711)** | In-vitro study | N / A | N / A | complex of collagen peptides and glycosaminoglycan oligosaccharides with molecular weights of 240-720 Da | N / A | Production of low MW compounds | Distribution of glycosaminoglycan sugars by the molecular weights in 6-h hydrolysates was in the range of 240-720 Da. Low molecular weight of the components increases their bioavailability and promotes assimilation in the human body. | In-Vitro Study |