

# Expedite™ Therapeutic Nutritional Drink for Wound Healing

## Key Research

### Dipeptides



Citation	Study Design	Patient Population	Groups	Outcomes
Jimi S, Koizumi S, Sato K, Miyazaki M, Saparov A. Collagen-derived dipeptide Pro-Hype administration accelerates muscle regenerative healing accompanied by less scarring after wounding on the abdominal wall in mice. <i>Sci Rep.</i> 2021;11(1):18750. doi:10.1038/s41598-021-98407-9.	Clinical trial; free drinking for 21 days	Mice with abdominal surgery	<ul style="list-style-type: none"> <li>○ Casein</li> <li>○ High molecular weight collagen peptides</li> <li>○ Low molecular weight collagen peptides, including Pro-Hyp and Hyp-Gly</li> </ul>	<b>Pro-Hyp administration accelerated muscle regenerative healing, accompanied by less scarring,</b> after wounding of the abdominal wall. Pro-Hyp could be administered to <b>patients with pressure injuries, who have undergone surgery or have trauma</b> to help activate the wound-healing process.
Lee SK, Posthauer ME, Dörner B, Redovian V, Maloney MJ. Pressure ulcer healing with a concentrated, fortified, collagen protein hydrolysate supplement: a randomized controlled trial. <i>Adv Skin Wound Care.</i> 2006;19(2): 92-96. doi:10.1097/00129334-200603000-00011.	Randomized trial for 8 weeks at 23 long-term care facilities in four states	89 residents with stage 2, 3, or 4 pressure injuries; 71 completed the study	<ul style="list-style-type: none"> <li>○ Standard care plus a concentrated, fortified, collagen protein hydrolysate supplement</li> <li>○ Standard care plus placebo</li> <li>○ Three times daily for 8 weeks</li> </ul>	<b>Residents who received standard care plus the concentrated, fortified, collagen protein hydrolysate supplement had significantly better PUSH tool scores</b> compared to those who had standard care plus placebo.
Sato K, Asai TT, Jimi S. Collagen-derived di-peptide, prolylhydroxyproline (Pro-Hyp): a new low molecular weight growth-initiating factor for specific fibroblasts associated with wound healing. <i>Front Cell Dev Biol.</i> 2020;8:543975. doi:10.3389/fcell.2020.548975.	Review	Animal studies and human clinical trials	<ul style="list-style-type: none"> <li>○ Pro-Hyp</li> </ul>	<b>Ingestion of collagen hydrolysate enhances wound healing,</b> especially diabetes-induced chronic wounds and pressure injuries. <b>Pro-Hyp is a low molecular weight growth-initiating factor for specific fibroblasts that are involved in the wound healing process.</b>
Skov K, Oxfeldt M, Thøgersen R, Hansen M, Bertram HC. Enzymatic hydrolysis of a collagen hydrolysate enhances postprandial absorption rate—a randomized controlled trial. <i>Nutrients.</i> 2019;11(5):1064. doi:10.3390/nu11051064.	Randomized, blinded, cross-over trial	Ten healthy males, ages 18-35 years	<ul style="list-style-type: none"> <li>○ EHC protein</li> <li>○ Non-EHC protein</li> <li>○ Placebo</li> <li>○ 3 nonconsecutive days</li> </ul>	<b>Enzymatic hydrolysis of collagen is associated with enhanced absorption of glycine, proline, and hydroxyproline</b> 20 minutes post-ingestion. Also, a greater AUC for glycine, proline, and hydroxyproline for an EHC hydrolysate suggested a <b>higher bioavailability for EHC compared to a nonenzymatically hydrolyzed collagen hydrolysate.</b>
Sugihara F, Inoue N, Venkateswarathirukumara S. Ingestion of bioactive collagen hydrolysates enhanced pressure ulcer healing in a randomized double-blind placebo-controlled clinical study. <i>Sci Rep.</i> 2018;8(1):11403. doi:10.1038/s41598-018-29831-7.	Double-blind, placebo-controlled clinical study	Subjects with pressure injuries, stage II or III; 112 subjects completed the study	<ul style="list-style-type: none"> <li>○ Low level Pro-Hyp and Hyp-Gly collagen hydrolysate</li> <li>○ High level Pro-Hyp and Hyp-Gly collagen hydrolysate</li> <li>○ Placebo</li> <li>○ 16 weeks</li> </ul>	<b>Collagen hydrolysate with higher levels of Pro-Hyp and Hyp-Gly helps heal pressure injuries</b> as measured by improvement in PUSH and PSST scores.

# Arginine and Citrulline

Citation	Study Design	Patient Population	Groups	Outcomes
Agarwal U, Didelija IC, Yuan Y, Wang X, Marini JC. Supplemental citrulline is more efficient than arginine in increasing systemic arginine availability in mice. 2017;147(4):596-602. doi:10.3945/jn.116.240382.	Randomized control trial	After recovery to presurgery body weight, 6-week-old mice were assigned to one of seven dietary treatment groups	<ul style="list-style-type: none"> <li>○ Arginine</li> <li>○ Citrulline</li> </ul>	<b>Citrulline supplementation is more efficient</b> at increasing arginine availability than is arginine supplementation itself in mice.
Khalaf D, Krüger M, Wehland M, Infanger M, Grimm D. The effects of oral L-arginine and L-citrulline supplementation on blood pressure. <i>Nutrients</i> . 2019;11(7):1679. doi:10.3390/nu11071679.	Review	Heterogenic study populations (small trials)	<ul style="list-style-type: none"> <li>○ L-arginine</li> <li>○ L-citrulline</li> </ul>	<b>Blood pressure-lowering effect was found</b> in meta-analyses for both L-arginine and L-citrulline; more research with larger study populations is needed to confirm these results.
Morita M, Hayashi T, Ochiai M, et al. Oral supplementation with a combination of L-citrulline and L-arginine rapidly increases plasma L-arginine concentration and enhances NO bioavailability. <i>Biochem Biophys Res Commun</i> . 2014;454(1):53-57. doi:10.1016/j.bbrc.2014.10.029.	Randomized trial	15 male rats (9 weeks old) and 9 male rabbits (8 weeks old) after 16-hour fast were given either L-citrulline, L-arginine, or a combination of each at half dosage	<ul style="list-style-type: none"> <li>○ L-arginine</li> <li>○ L-citrulline</li> </ul>	<b>Combination of L-citrulline and L-arginine effectively and rapidly augments. NO-dependent responses at the acute phase.</b> May have clinical utility for the regulation of cardiovascular function in humans.
Shatanawi A, Momani MS, Al-Aqtash R, Hamdan MH, Gharaibeh MN. L-citrulline supplementation increases plasma nitric oxide levels and reduces arginase activity in patients with type 2 diabetes. <i>Front Pharmacol</i> . 2020;11:584669. doi:10.3389/fphar.2020.584669.	Clinical study	25 patients with type 2 diabetes on oral hypoglycemic drugs	<ul style="list-style-type: none"> <li>○ L-citrulline for 1 month</li> </ul>	<b>L-citrulline can have therapeutic benefits in patients with diabetes</b> through increasing NO levels and maintaining vascular function, possibly through an arginase inhibition-related pathway.
Wijnands KAP, Vink H, Briedé JJ, et al. Citrulline a more suitable substrate than arginine to restore NO production and the microcirculation during endotoxemia. <i>PLoS One</i> . 2012;7(5):e37439. doi:10.1371/journal.pone.0037439.	Randomized trial	65 male mice received an 18-hour IV infusion of endotoxin combined with either L-citrulline, L-arginine, or L-alanine (isonitrogenous control) during the last 6 hours; control group received sterile saline combined with L-alanine or L-citrulline during the last 6 hours	<ul style="list-style-type: none"> <li>○ L-alanine (control)</li> <li>○ L-arginine</li> <li>○ L-citrulline</li> </ul>	<b>L-citrulline supplementation during endotoxemia positively influenced the intestinal microvascular perfusion</b> compared to L-arginine supplemented and control endotoxemic mice. <b>L-citrulline supplementation</b> (and not L-arginine supplementation) <b>during murine endotoxemia improves the microcirculation and results in increased plasma and tissue availability</b> of citrulline, arginine, and NO during endotoxemia.

AUC=area under the curve, EHC=enzymatically hydrolyzed collagen hydrolysate, IV=intravenous, Pro-Hyp=prolylhydroxyproline, Hyp-Gly=hydroxyprolylglycine, NO=nitric oxide, PUSH=Pressure Ulcer Scale for Healing, PSST=Pressure Sore Status Tool