Hypertension affects 30% of adults in the US and increases the risk for heart disease and stroke, the first and third leading causes of death in this country\(^1\). In addition, pre-hypertension, associated with poor sleep, excess weight and insulin resistance, affecting 70 million Americans, is thought to increase the risk of a heart attack by 3 times. Prehypertension usually develops into full blown hypertension if untreated\(^2\). Recent guidelines define prehypertension or high normal blood pressure for systolic blood pressure (SBP) in the range of 120-139 mmHg and diastolic blood pressure (DBP) in the 80-89 mmHg range, while hypertension is defined as having a SBP starting at 140 mmHg and a DBP starting at 90 mmHg\(^3\). AmealPeptide\(^\circledR\) is a naturally occurring, safe, and highly effective blood pressure lowering ingredient derived from a component of milk protein known as casein. It occurs in very small amounts in casein as tripeptides which are 3 specific amino acids joined together in a precise configuration. It works to lower blood pressure by inhibiting the angiotensin converting enzyme (ACE) and is otherwise known as an ACE inhibitor that many pharmaceuticals are based on. Angiotensin I is converted to angiotensin II via the ACE produced by the vascular endothelium. ACE inhibitors decrease the formation of angiotensin II and the metabolism of bradyquin, resulting in the dilation of arteries and veins and the lowering of arterial blood pressure.

The two tripeptides in AmealPeptide\(^\circledR\) are known as the lactotripeptides, Valyl-Prolyl-Proline (VPP) and Isoleucyl-Prolyl-Proline (IPP), derived from the three dietary amino acids: valine, proline, and isoleucine. These are manufactured by enzymatically hydrolyzing casein in a precise manner with the protease derived from Aspergillus oryzae in such a way that the peptides are not damaged or broken down into their individual amino acids. They are also not degraded in the human digestive system because of their precise configuration and can be absorbed intact to be physiologically active. These lactotripeptide combinations are not found in enough quantities in common foods unless treated with the proprietary processes used to make AmealPeptide\(^\circledR\). The efficacy of AmealPeptide\(^\circledR\) unlike other untested milk peptides has been evaluated in numerous randomized, placebo-controlled human clinical trials for hypertension and pre-hypertension.

In a study using 4 mg of the lactotripeptides (VPP, IPP) with a placebo-controlled, double-blinded design, the hypotensive effects of 42 subjects with mild or moderate untreated hypertension were given 2 tablets (each tablet having 1.26 mg of VPP and 0.82 mg of IPP or 4 mg total) once a day at breakfast for 8 weeks with 39 in the placebo group. In the test group, SBP decreased significantly in prehypertensive and hypertensive subjects after 2 weeks and 8 weeks of treatment, by 7.4 +/- 9.6 mmHg and 12.4 +/- 10.9 mmHg, respectively, and DBP decreased significantly after 2 weeks and 8 weeks of treatment, by 6.7 +/- 13.2 mmHg and 8.1 +/- 12.7 mmHg, compared to pretreatment. In the placebo group, no changes were detected and the treatment group showed no adverse effects\(^5\).

A randomized, double-blind, placebo-controlled study used 3 mg of the casein hydrolyzed tripeptide given to 72 subjects out of a total of 144 subjects having high-normal blood pressure or pre-hypertension (104) and mild hypertension (40). The VPP and IPP casein triptides added to a test drink were found to have blood pressure lowering effects. One group ingested a 200 ml bottle of the test drink at breakfast, while a group of 72 people took the placebo drink. The 200 ml quantity of test drink contained 1.47 mg of Val-Pro-Pro and 1.60 mg of Ile-Pro-Pro or 3.07 mg total. Subjects were randomly assigned to two groups for a 12-week intake period. In the test group, both SBP and DBP decreased significantly compared with the placebo group: SBP/DBP significantly decreased from 138.2 +/- 6.5/84.4 +/- 5.3 at the beginning to 132.3 +/- 7.3, and 81.2 +/- 4.8 mmHg at the 12th week. On average, the SBP dropped 5.9 mmHg while the DBP dropped 3.3 mmHg. In analyzing the data, antihypertensive effects were found in both the pre-hypertensive group and those with actual mild hypertension. No adverse effects were observed in any subjects in the study\(^6\).

In a placebo-controlled, double-blind parallel group study, a dosage of 3.55 mg per day of the lactotripeptides (Val-Pro-Pro, Ile-Pro-Pro) was used for 12 weeks in 111 subjects (68 male and 43 female) from ages 30 to 70 with an average age of 51. The subjects had either high-normal blood pressure or mild hypertension with the average SBP/DBP of 138.8 ± 7.6 and 91.8 ± 8.9 mmHg. Subjects were randomly divided into two groups. The test group ingested daily 4 test tablets (1.4 g) containing 1.28 mg VPP and 2.27 mg IPP while the other group ingested the same amount of placebo tablets for 12 weeks.

The systolic blood pressure was significantly reduced beginning at 4 weeks time in the test group, and was significantly lower compared with the placebo group at 2, 4, 8, 10, 12 and 14
weeks in both prehypertensive and mild hypertensive groups. Compared to the value on the day of starting ingestion, SBP dropped 7.9 ± 8.4 mmHg after 12 weeks in the test group with mild hypertension. Subjects in the test group with prehypertension exhibited significantly lower values of SBP 2, 8, 10, 12 weeks after starting ingestion than the placebo group, values falling 9.8 ± 8.1 mmHg 12 weeks after starting. The estimated sodium excretion in daily urine of the test group showed a significant decrease in comparison between two groups. No abnormal changes were found in the blood and urinary analysis, and no adverse events such as dry cough were found.

The bioavailability of one of the lactotripeptides found in AmealPeptide®, Ile-Pro-Pro, was determined in 6 male and female subjects who randomly consumed the enriched yogurt beverage or a placebo while fasting or after a meal. The area under the curve (AUC) of Ile-Pro-Pro peptide after the LTP treatment in the fasted state was 2.1-fold of the placebo treatment (P < 0.001). Meal intake affected Ile-Pro-Pro concentrations. When the beverage was consumed after a meal, the AUC of Ile-Pro-Pro was 1.3-fold greater than the AUC of the premeal dose. This was due to an increase in the plasma elimination half-life which may help more of the peptide to be maintained if consumed with food. The study revealed that the tripeptide, Ile-Pro-Pro, selectively escapes from digestion and intestinal degradation, reaching the circulation without being broken down.

In a randomized, double-blind, placebo-controlled clinical trial, the effect of a 3.4 mg dosage of the milk-derived peptides, VPP and IPP, on central blood pressure and arterial stiffness was investigated in 70 Japanese subjects aged 50-69 years with untreated stage-1 hypertension. Participants were randomly assigned to two groups, which received either placebo tablets or active tablets containing 3.4 mg of VPP and IPP. Central blood pressure and brachial-ankle pulse wave velocity, a marker of arterial stiffness, were both measured at the beginning and end of the 8-week study. A 6.5 mm Hg difference in central systolic blood pressure between the treatment group and placebo group was observed. The reduction in brachial-ankle pulse wave velocity was 73.9±130.0 for the treatment group compared to 8.4±137.1 cm/s for the placebo group. The brachial SBP decreased by 10.5±11.5 in the active group versus 3.9±9.6 mmHg in the placebo. The drop in radial mean blood pressure of 7.3±8.9 compared to 2.0±7.4 mmHg in the placebo was significant too. Overall, the results show that casein hydrolysate containing VPP and IPP improves central SBP and brachial-ankle pulse wave velocity in hypertensive subjects demonstrating beneficial effects on arterial health such as reduced arterial stiffness and reduced blood pressure.

The blood pressure lowering benefits of AmealPeptide® in prehypertension and stage 1 hypertension is well documented with several studies showing it to reduce systolic blood pressure between 6 to 10 mmHg and diastolic BP from 3 to 8 mmHg, depending on if the condition was prehypertension or hypertension. AmealPeptide® has a blood pressure reducing mechanism of action through ACE inhibition and reduces arterial stiffness. Safely derived from milk protein through a special enzymatic proprietary process, AmealPeptide® is GRAS for inclusion in food and beverages as well as dietary supplements.

REFERENCES