MAKE WELLNESS LEAN

with APTICURB TRIMFAST COMPLEX:

by

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Make Wellness LEAN featuring the AptiCurb TrimFast Complex

A New Generation of Nutrition Technology

Abstract: The emergence of chronic diseases has become a global health concern, with their prevalence rising considerably in recent years. Obesity is one such chronic disease whose prevalence has risen significantly over the past few years. Bioactive precision peptides and bioactive flavonoid-rich polyphenolic compounds have many possible uses in nutritional science. A bioactive precision peptide matrix of peptides less than 10kDA molecular weight combined with bioactive flavonoid-rich polyphenolic compounds has tremendous potential to modify the physical parameters of obesity. New processing technology has also been developed to protect and preserve bioactive precision peptides' physiological activity and bioavailability in protein hydrolysates. Make Wellness LEAN is a weight management tool that combines bioactive precision peptides and bioactive flavonoid-rich polyphenolic compounds to influence mechanisms of action that improve human body composition. This literature review will describe the structural characteristics and physiologic benefits of bioactive precision peptides derived from hydrolyzed yeast protein and bioactive flavanone and phenolic compounds derived from citrus fruits and guarana. It will detail the importance of the hydrolysis process in preserving the form and function of bioactive precision peptides and the protective mechanism of the protein-peptide matrix. Lastly, it will discuss the mechanisms of action and clinical benefits of bioactive precision peptides combined with bioactive flavonoid-rich polyphenolic compounds to improve weight control through lipolysis, thermogenesis, and appetite regulation.

Introduction

Obesity is a chronic condition that is rapidly growing in Western cultures. In adults over 20, the prevalence of obesity is more than 41.9%, with severe obesity affecting 9.2% of all adults over 20 (CDC.GOV). Alarmingly, the prevalence of obesity climbed from 30.5% in 2000 to 41.9% in 2020 and continues to rise. Obesity is a worldwide epidemic that presents a tremendous burden to the healthcare system (Dallas et al., 2008). Obesity-related chronic conditions accounted for more than $173 billion in medical expenditures in 2019. 58% of obese adults have hypertension, and 23% have diabetes. Other chronic conditions associated with obesity are chronic pain and osteoarthritis, asthma, sleep apnea, gallbladder disease, stroke, cancer, mental illness, and premature death (CDC.GOV).

While excess body fat is the primary characteristic of obesity, it is also associated with low-grade systemic inflammation and chronic inflammatory response characterized by activation of proinflammatory signaling pathways and abnormal markers of inflammation, including C-reactive protein and fibrinogen (Dallas et al., 2014). Chronic inflammation leads to increased insulin resistance and muscle breakdown, further contributing to the deleterious effects of chronic obesity (Damluji et al., 2023). As muscle mass progressively declines with increased obesity and chronic inflammation, so does basal metabolic rate, leading to increased adiposity and fatty infiltration in skeletal muscle, bone marrow, and the liver. Loss of muscle mass leads to a loss of metabolic fitness.

Bioactive precision peptides (BPPs) and bioactive flavonoid-rich polyphenolic compounds (BFPCs) are naturally occurring biologically active chemicals with enormous potential for facilitating human health. Compared to pharmaceutical weight loss drugs, BPPs and BFPCs have fewer side effects, significantly lower toxicity, and much less impact on lean muscle

mass (Ahn et al., 2021; Cases et al., 2015; Dallas et al., 2014; Jung et al., 2014; Prado et al., 2024). They are particularly beneficial for improving body composition and metabolic health. Many individuals concerned with the potential short and long-term adverse effects of synthetic pharmaceutical options prefer the use of naturally derived BPPs and BFPCs to safely and effectively combat and prevent obesity and reduce the incidence of chronic diseases.

Structure and Function of Bioactive Precision Peptides

BPPs are specific small amino acid fragments, generally 2-20 amino acids long, obtained from natural plant and animal sources and capable of eliciting a physiochemical change beyond their nutritional value in normal body processes (Abeer et al., 2021; Purohit et al., 2024). Protein-based foods contain numerous BPPs that act as functional agents, offering numerous potential health benefits analogous to endogenous signaling molecules that influence physiological processes. Recent research has demonstrated the significance of BPPs as physiologically active and therapeutically beneficial compounds.

BPPs have high oral bioavailability and are vital to human physiology, primarily acting as signaling agents that modulate physiological processes such as growth, including muscle and bone development, immunomodulation, inflammation, antioxidant potential, and gene regulation (Purohit et al., 2024; Xavier et al., 2024). The high tissue affinity of BPPs influences the mechanisms by which they interact with receptors, enzymes, and specific biomolecules within the body to precisely influence physiological processes. Their high specificity, potency, and inherent beneficial properties have led to the discovery and development of many safe, tolerable, and efficacious peptide therapies and nutritional supplements. More than 60 bioactive peptide-based medications have been developed, with another 500 plus currently in some stage of development, further highlighting their therapeutic potential to enhance human well-being.

Naturally derived, bioactive precision peptides are at the cusp of revolutionizing health and nutritional science (Zhou et al., 2024). Make Wellness LEAN contains a matrix of BPPs of less than 10kDa molecular weight derived from a yeast protein hydrolysate of Saccharomyces cerevisiae.

Method of Production of BPPs

Protein hydrolysates of plant and animal origin are recognized as a viable source of releasable mixtures of BPPs with potential health benefits. Protein hydrolysates are also known as predigested hydrolyzed proteins and are mixtures of peptides and amino acids produced by the hydrolysis of proteins. BPPs are cleaved from hydrolysates during digestion by stomach pepsin and proteases to produce bio-accessible low-molecular-weight peptides. The critical determinants of BPPs physiological activity include their amino acid (AA) constituents, the nature of the AAs contained in the peptide chain, the AA residues at the N and C termini of the peptides, the molecular weight, structure, and physiochemical properties (Xavier et al., 2024). The AA sequence and composition of the peptides determine their activity once they are released from the protein-peptide matrix within which they are encrypted (Sanchez & Vázquez, 2017). Proteins of plant and animal origins are potential sources of a wide range of BPPs encrypted in their structure. To successfully produce BPPs, apart from selecting the appropriate protein source and proteases, the conditions of the hydrolysis process are of great significance. The degree of hydrolysis achieved in the isolation and concentration of BPPs significantly influences the bioavailability of the specific peptides (Xavier et al., 2024). The detection quality parameters for the industrial hydrolysis process include controlling the ratio of amino nitrogen to total nitrogen to determine the degree of hydrolysis, the content of free amino acids and total amino acids in the hydrolysate, and the molecular weight distribution of peptides (Dullius et al., 2020). Protein

source, type of protease, the molecular weight of the peptides, and conditions of the hydrolysis process, including peptidases, the substrate-to-peptidase ratio, temperature, pH, and reaction time are also critical to preserving the function and bioavailability of the BPPs (Xavier et al., 2024). Protease-catalyzed enzyme hydrolysis utilizes different proteases that cleave proteins at specific amino-acid sites and maintain the integrity of other peptide bonds (Purohit et al., 2024). Using the correct enzyme with high specificity and maintaining adequate controls over the hydrolysis process parameters is crucial to producing BPPs with the required physiological and functional properties.

Absorption and Transport

Because BPPs are smaller than proteins, they are more bioavailable and less allergenic. Unlike synthetic therapeutic peptides, which are highly unstable, broken down during digestion, and typically must be injected, food-derived BPPs are gentler, safer, and more easily absorbed (Xavier et al., 2024). To facilitate absorption, BPPs are transported across the intestinal brush-border membrane into the bloodstream via both active and passive routes. There are four main pathways by which bioactive peptides enter the blood across the intestinal epithelial cell monolayer, including peptide transporter-mediated transport, the paracellular route across tight junctions, transcytosis, and passive transcellular diffusion (X. Zhu et al., 2023). There are two known peptide transporters: H+-coupled PepT1 and Na+-coupled SOPT1 and SOPT2. PepT1 is specific to di and tripeptides, preferentially recognizing short hydrophobic, nonpolar peptides with neutral charges. SOPT1 and SOPT2 transport oligopeptides containing at least five amino acids.

The paracellular pathway in the human gastrointestinal tract is regulated by paracellular diffusion pores called tight junctions that are mainly composed of occludin, zonula occludens-1,

and claudin proteins, which form a tight barrier with selective penetration (Xu et al., 2019). The presence of tight junctions explains the higher bioavailability of small peptides when compared to larger peptides or proteins. Due to the limited size and electrostatic properties of tight junctions, hydrophilic and negatively charged low molecular weight peptides are preferentially transported via paracellular pathways. Transcytosis involves apical endocytic uptake via internalization, transcytotic vesicle transport, and basolateral secretion and is an energy-dependent transcellular pathway. Highly hydrophobic and long-chain peptides with more than ten amino acids are usually absorbed through this pathway because hydrophobic BPPs must interact with the apical lipid surface via hydrophobic interactions prior to internalization. Passive transcellular diffusion involves passive uptake into cells, intracellular transport, and basolateral effusion and is the transport mechanism for positively charged and hydrophobic macromolecular peptides. Transport of BPPs via this route is influenced by many factors, including their size, charge, and hydrophobicity. The BPPs in LEAN are transported by two critical transport systems: the peptide transporter-mediated transport mechanism and the paracellular transport mechanism across tight junctions in a receptor-mediated manner, as determined by their overall charge, molecular mass, hydrophobicity, and aggregation tendency (Guha et al., 2021; Yu et al., 2024).

Significance of Encryption

BPPs are encrypted and protected within larger protein-peptide matrixes and do not become active until they are released by hydrolysis (Shea et al., 2024). The encryption of the BPPs impacts stability and bioavailability by protecting the structural and functional integrity of the BPPs. The peptide bonds of BPPs are shielded from enzymatic degradation by the protective barrier provided by the protein peptide matrix, thus increasing their stability through the GI tract (Zaky et al., 2022). The protein-peptide matrix also allows for a controlled release of the BPPs

from the protein-peptide matrix, which increases and prolongs the bioavailability of the BPPs (Purohit et al., 2024). Because the BPPs are part of a more significant protein or peptide fragment, BPPs can be absorbed more efficiently than individual, unprotected peptides. The protein carrier can also facilitate transport across the intestinal barrier while buffering BPPs against pH changes in the digestive system, which further preserves structure and function (Zaky et al., 2022). Notably, the protein-peptide matrix preserves biological activity by shielding the BPPs from oxidation and allowing for a more targeted delivery of the BPPs to specific sites within the body before they are released.

Structure and Function of Bioactive Flavonoid-Rich Polyphenolic Compounds

The BFPCs in Lean are derived from grapefruit, sweet orange, blood orange, and guarana extracts (Park et al., 2020; Yoo JM, 2016). These extracts are rich in bioactive compounds, particularly flavonoids and polyphenols. Flavonoids have a basic structure of two aromatic rings linked by a three-carbon chain (Mutha et al., 2021). Common citrus flavonoids include hesperidin, naringin, and nobiletin. Polyphenols are compounds with a phenol ring and an organic carboxylic acid function. The bioactive functions of citrus phenolic compounds generally include antioxidant activity, anti-inflammatory effects, metabolic regulation, and enzyme inhibition. Phenolic compounds can neutralize free radicals and reduce oxidative stress (Rana et al., 2022). Many phenolics have been shown to modulate inflammatory pathways. Some citrus phenolics may influence lipid and glucose metabolism. Certain phenolic compounds can inhibit specific enzymes involved in various metabolic processes. The bioactivity of these compounds often relates to their chemical structure, particularly the number and position of hydroxyl groups on the aromatic rings (Rana et al., 2022).

The primary bioactive flavanones in Lean are naringin and hesperidin. Naringin is a flavanone glycoside that consists of naringenin attached to a disaccharide (Dias et al., 2021). Naringin has anti-inflammatory, antioxidant, and lipid-lowering effects (Dallas et al., 2014). It may help regulate glucose metabolism and has been studied for its potential anti-diabetic properties. Hesperidin is also a flavanone glycoside, which consists of the flavanone hesperetin linked to a disaccharide (Dias et al., 2021). Hesperidin exhibits antioxidant and anti-inflammatory properties. It has been associated with cardiovascular protection and may assist in long-term body composition management. Another flavone found in LEAN is nobiletin. Nobiletin is a polymethoxylated flavone that has been studied for its potential anti-inflammatory and metabolic effects (Dias et al., 2021). It may play a role in lipid metabolism and glucose regulation.

Significance of BPPs and BPFCs in Human Health

BPPs are derived from natural plant and animal protein sources and are released through enzymatic hydrolysis during digestion or from hydrolyzing protein sources with specific proteolytic enzymes (Purohit et al., 2024). BPPs are inactive in their native states but exhibit powerful physiologic effects when unlocked from their protective protein-peptide matrix. BPPs generally have a broader physiologic effect on overall health and wellness and chronic disease prevention compared to therapeutic peptides due to the likelihood of influencing multiple mechanisms of action (Shahnaz et al., 2024). In addition, BPPs do not have side effects and represent a safe and beneficial alternative to many of the drugs currently used to treat chronic diseases.

BPPs have demonstrated the ability to influence multiple physiological functions, including enhancing muscle protein synthesis, preventing fatigue, and promoting brain health.

BPPs also possess anti-inflammatory, antioxidant, antidiabetic, antigout, antihypertensive, immunomodulatory, antimicrobial, and cholesterol-lowering capabilities (Li et al., 2023; F. Zhu et al., 2023). As dietary interventions, these food-derived functional factors possess incomparable advantages over drugs, including early prevention, safety, effectiveness, and a lack of ideological and economic burden (Li et al., 2023). The stability and half-life of BPPs also impact their physiological benefits, with the presence of prolines embedded within the peptide sequences enhancing stability through digestion and absorption and peptides containing threonine at the N-terminus exhibiting a prolonged half-life in biological matrices (Corrochano et al., 2021).

BPFCs are naturally occurring substances found abundantly in fruits, vegetables, herbs, and other plant-based foods that have been the subject of extensive research for their diverse range of biological activities and potential therapeutic applications (Dias et al., 2021). BFPCs are a diverse group of plant secondary metabolites characterized by their polyphenolic structure. They typically consist of two or more aromatic rings, each bearing at least one hydroxyl group (Rana et al., 2022). Flavonoids, a major subclass of polyphenols, are further categorized into several groups, including flavonols, flavones, flavanones, isoflavones, anthocyanidins, and flavan-3-ols.

The structural diversity of BFPCs contributes to their wide range of biological activities. The number and position of hydroxyl groups, the degree of glycosylation, and other structural features can significantly influence their bioavailability, antioxidant capacity, and interactions with cellular components (Rana et al., 2022). One of the most well-established benefits of BFPCs is their potent antioxidant activity. Oxidative stress, caused by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them, is

implicated in numerous chronic diseases and the aging process. BFPCs can act as direct scavengers of free radicals, chelate metal ions that catalyze oxidation reactions, and upregulate endogenous antioxidant defense systems.

Chronic inflammation is a common underlying factor in many diseases, including cardiovascular disease, diabetes, and cancer. BFPCs have shown significant anti-inflammatory properties through various mechanisms (Dias et al., 2021; Rana et al., 2022). They can modulate the activity of pro-inflammatory enzymes such as cyclooxygenase and lipoxygenase, inhibit the production of inflammatory cytokines, and suppress the activation of nuclear factor-κB, a key transcription factor in inflammatory responses.

The beneficial effects of BFPCs on cardiovascular health have been well-documented (Mutha et al., 2021). These compounds can improve endothelial function, reduce blood pressure, inhibit platelet aggregation, and modulate lipid metabolism. One mechanism by which BFPCs promote cardiovascular health is by enhancing nitric oxide (NO) bioavailability. NO is a crucial vasodilator that helps maintain healthy blood pressure and vascular function. Flavonoids can increase NO production and reduce its degradation, thereby improving endothelial function and blood flow.

BFPCs play a significant role in metabolic health, particularly in the context of obesity and type 2 diabetes. These compounds can modulate glucose metabolism, improve insulin sensitivity, and regulate lipid metabolism (Mutha et al., 2021). For example, anthocyanins found in berries have been shown to improve glucose tolerance and insulin sensitivity in both animal and human studies. Moreover, certain BFPCs have demonstrated the ability to influence body weight and fat accumulation. Naringin and hesperidin, both found in LEAN, play significant

roles in metabolic function, including lipid-lowering lipolytic benefits and uncoupled oxidative phosphorylation (Lee et al., 2017).

The importance of BFPCs to human health cannot be overstated. These compounds offer many health benefits, from their potent antioxidant and anti-inflammatory properties to their potential in preventing and treating chronic diseases (Rana et al., 2022). As our understanding of their mechanisms of action and bioavailability grows, BFPCs hold promise for developing novel nutraceuticals and therapeutic strategies with targeted applications in personalized nutrition and medicine, contributing to improved health outcomes and quality of life for many individuals.

LEAN Mechanisms of Action

Lean is comprised of a combination of BPPs and BFPCs that impart multiple mechanisms of action on the body, including enhanced lipolysis, increased free fatty acid utilization, increased resting energy expenditure, increased beiging of white adipose tissue, modulation of satiety hormones, and decreased release of neuropeptide Y from the hypothalamus. The BPPs in LEAN are derived from a yeast protein hydrolysate of Saccharomyces cerevisiae. Studies have demonstrated multiple mechanisms of action explaining the effectiveness of yeast protein hydrolysate in managing weight-control issues. The BFPCs in LEAN are derived from various citrus fruits and guarana and have been shown to have multiple mechanisms of action for supporting fat loss, including enhanced lipolysis, increased metabolic rate, and potential improvements in glucose metabolism and adipokine production.

A study by Kim et al. (2023) investigated the effects of the yeast protein hydrolysate used in LEAN on fat accumulation during adipocyte differentiation. The research demonstrated that at a concentration of 2 mg/mL, yeast protein hydrolysate significantly reduced lipid accumulation

in adipocytes, as evidenced by decreased Oil Red O-stained lipids. This effect was accompanied by changes in gene expression, with yeast protein hydrolysate downregulating early adipogenic factors like C/EBPβ and upregulating KLF2 while also decreasing the expression of later-stage adipogenic genes such as C/EBPα, PPARγ, and FABP4. Furthermore, the study revealed that yeast protein hydrolysate significantly downregulated SREBP1c and SREBP2, key transcription factors controlling fatty acid and cholesterol metabolism, with a more pronounced effect on SREBP1c (Kim et al., 2023). The yeast protein hydrolysate also reduced the expression of their target genes, including FAS, ACC, and HMGCR. Additionally, yeast protein hydrolysate decreased the mRNA levels of G6PD and malic enzyme, which are involved in NADPH synthesis for lipid production, further contributing to its anti-adipogenic effects.

Another crucial finding of the study was identifying 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA) as an additional bioactive compound in yeast protein hydrolysate responsible for its anti-adipogenic effects (Kim et al., 2023). MTCA, at a concentration of 1.1 μg/mL, significantly downregulated SREBP1c and SREBP2 mRNAs and their target genes. SREBP1c and SREBP2 are key transcription factors controlling fatty acid and cholesterol metabolism. These results suggest that the yeast protein hydrolysate used in LEAN can effectively suppress adipogenic lipid storage by downregulating SREBP- and NADPH-synthesizing genes (Kim et al., 2023).

A study by Lee et al. (2017) investigated the effects of the BFPCs in LEAN on lipolysis in leptin-deficient obese (ob/ob) mice. The researchers treated obese mice with two doses of BFPCs (100 mg/kg and 300 mg/kg of body weight) for seven weeks. The study focused on examining the impact of BFPCs on lipolysis in this specific genetic model of obesity, which is commonly used in obesity research due to the mice's predisposition to excessive weight gain.

The results showed that low and high doses of BFPCs reduced body weight gain in obese mice compared to the control group. Additionally, abdominal and visceral adipose tissue weights were reduced in the high-dose group, while epididymal adipose tissue weight decreased in both low and high-dose groups by 18.27% and 41.05%, respectively (Lee et al., 2017). The study also observed changes in gene expression related to lipolysis. Phosphodiesterase 3B (PDE3B) mRNA levels decreased with BFPC supplementation, while A-kinase anchor protein 1 (AKAP1), adipose triglyceride lipase (ATGL), and perilipin (PLIN) mRNA levels increased. These findings suggest that BFPC supplementation partially stimulates lipolysis by reducing PDE3B and inducing AKAP1, ATGL, and PLIN gene expression, reducing body and white adipose tissue weight, particularly in cases of leptin deficiency.

A study by Yoo et al. (2016) investigated the effects of the BFPCs in LEAN on leptin-deficient obese (ob/ob) mice and its impact on cAMP-dependent uncoupling protein 2 (UCP-2) activation. The research focused on a specific genetic model of obesity, using leptin-deficient mice to examine how the BFPCs in LEAN might influence body weight and fat metabolism in the absence of leptin signaling. Notably, the researchers observed activation of cAMP-dependent UCP-2, a protein involved in energy metabolism (Yoo JM, 2016). This observation suggests that the BFPC's anti-obesity effects may be mediated by activating UCP-2 via a cAMP-dependent signaling pathway. The activation of UCP-2 contributes to weight loss through several interconnected mechanisms related to energy metabolism and fat oxidation (Hatami et al., 2024). UCP-2 functions in the inner mitochondrial membrane at its core, increasing proton leak and partially uncoupling oxidative phosphorylation from ATP synthesis. This uncoupling increases energy expenditure as heat rather than ATP production, leading to a higher metabolic rate and increased resting energy expenditure. Therefore, more calories are burned to maintain the same

level of ATP production, contributing to weight loss (Yoo JM, 2016). Additionally, UCP-2 activation stimulates the use of fatty acids as an energy source, enhancing fat oxidation and helping to reduce stored body fat.

UCP-2 activation regulates ROS production in mitochondria, affecting cellular metabolism and stress responses. UCP-2 activation has also been associated with improved insulin sensitivity, potentially leading to more efficient glucose metabolism and reduced fat storage (Hatami et al., 2024). Furthermore, UCP-2 may play a role in the hypothalamic regulation of food intake, potentially leading to reduced appetite and food consumption. UCP-2 activation also has broader impacts on metabolic health that can indirectly contribute to weight loss. It may stimulate mitochondrial biogenesis, increasing mitochondrial density and enhancing overall metabolic capacity. UCP-2 has been implicated in the regulation of inflammatory processes, with reduced inflammation contributing to improved metabolic health. UCP-2 activation can influence lipid metabolism in the liver, potentially reducing hepatic steatosis often associated with obesity. While UCP-1 is more commonly associated with brown adipose tissue, UCP-2 activation may also enhance the thermogenic capacity of white adipose tissue (Hatami et al., 2024). This mechanism provides insight into how the BFPCs in LEAN work at a molecular level to influence obesity via the specific molecular pathway of cAMP-dependent UCP-2 activation.

Jung et al. (2012) investigated the effects of yeast protein hydrolysate on hepatic lipid metabolism in mice with diet-induced obesity to determine if its anti-obesity activity was due to the alteration of lipid-regulating enzyme activities. The research utilized a high-fat-diet-induced obesity model in mice, dividing them into four groups: a normal diet group, a high-fat diet group, and two high-fat diet groups treated with different concentrations of yeast protein hydrolysate

(0.5% and 1%) in drinking water for five weeks. The study demonstrated that yeast protein hydrolysate supplementation significantly reduced epididymal fat levels, serum triglycerides, and low-density lipoprotein cholesterol concentrations compared to the high-fat diet group. Additionally, yeast protein hydrolysate supplementation led to a decrease in body weight gain and a dose-dependent increase in serum ghrelin levels. The research focused on the effects of yeast protein hydrolysate on hepatic lipid metabolism, specifically examining its influence on body fat accumulation and fatty acid synthesis. The mechanism of action was explored through the examination of hepatic enzyme activities. Yeast protein hydrolysate supplementation inhibited hepatic glucose-6-phosphate dehydrogenase (G6PD) activity and significantly decreased hepatic malic enzyme (ME) activity in the 1% yeast protein hydrolysate group compared to the high-fat diet group ($p<0.05$). These findings suggest that yeast protein hydrolysate suppresses body fat accumulation by attenuating fatty acid synthesis by downregulating hepatic G6PD and ME activities.

Jung et al. (2009) investigated the effects of peptides of less than 10 kDa (BY1 (0.1g/kg) and BY2 (1.0 g/kg)) and peptides between 10-30 kDa (AY1 (0.1 g/kg) an AY2 (1.0 g/kg)) molecular weight derived from yeast protein hydrolysate on neuropeptide Y (NPY) and tryptophan hydroxylase (TPH) immunoreactivity in rats. The research focused on two important neurotransmitter systems: NPY, which is involved in appetite regulation and energy balance, and TPH, a key enzyme in serotonin synthesis. This focus allowed the researchers to explore potential neurochemical mechanisms by which yeast protein hydrolysate might influence appetite and metabolism. The study's results indicate that administering yeast protein hydrolysate with peptide sizes below 10 kDa to normal diet-fed rats reduced body weight gain and serum lipids by altering NPY and TPH expressions. Body weight gains were lower in the BY groups

(oral administration of yeast hydrolysate below 10 kDa) than in the control group (Jung et al., 2009). In particular, body weight gain was significantly ($p < 0.05$) lower in the BY2 group (133.0 g) than in the control group (150.1 g). The AY groups demonstrated tendencies of high weight gain compared to control. Triacylglyceride, total cholesterol, and LDL-cholesterol levels were significantly ($p < 0.05$) lower in the BY-2 group as compared to the control (Jung et al., 2009). NPY neuron-staining intensities at the paraventricular nucleus were significantly lower ($p < 0.05$) in the BY groups (BY-1: 96.1, BY-2: 88.6) as compared to the control (105.6) and AY groups (AY-1: 110.5, AY-2: 114.1), however, there was no significant difference between the BY-1 and BY-2 group. NPY expression at the lateral hypothalamic area was significantly lower ($p < 0.05$) in the BY-2 group than in the other groups. In the AY groups, NPY neuron staining intensities at the lateral hypothalamic area region were significantly ($p < 0.05$) higher (AY-1: 107.3, AY-2: 110.8) as compared to the control group (98.9). TPH expression was significantly ($p < 0.05$) lower in the AY-2 group (115.9) than in the control group (141.4) and BY groups (BY-1: 143.9, BY-2: 154.6). The results of the present study demonstrate that administering yeast hydrolysate of below 10 kDa to rats produced significant dose-dependent reductions in body weight gain, serum triacylglyceride, total cholesterol, and LDL-cholesterol levels (Jung et al., 2009). Changes in NPY levels could indicate effects on appetite regulation and energy metabolism, while alterations in TPH immunoreactivity might suggest impacts on serotonin synthesis, potentially affecting mood and appetite. This research contributes to our understanding of how yeast-derived products could affect brain chemistry related to eating behavior, adding a neurobiological perspective to the growing body of research on yeast hydrolysate's potential health benefits.

A study by Dallas et al. (2008) investigated the lipolytic effects of the BFPCs in LEAN on human fat cells (adipocytes). The study aimed to elucidate the mechanism of action behind the LEAN BFPCs fat-reducing properties. First, the study investigated the lipolytic effect of BFPCs in human adipocytes by measuring free fatty acid (FFA) release. Second, the study examined the potential of a daily intake of 1.4 g of BFPCs in decreasing body fat and body mass index (BMI) in healthy human subjects. Third, BFPCs were tested for their ability to inhibit cAMP-PDE (Dallas et al., 2008). Twenty healthy, drug-free male and female volunteers between 25 and 55 years with a BMI between 27 and 33 participated in a randomized, placebo, double-blinded trial protocol. The intervention group ingested 350 mgs of BFPCs twice daily for 12 weeks. The study's key findings demonstrated that the BFPCs contained in LEAN had a significant lipolytic (fat-breaking) effect on human adipocytes, primarily achieved through the inhibition of cAMP-phosphodiesterase (PDE) (Dallas et al., 2008). By inhibiting PDE, these BFPCs increase intracellular levels of cyclic AMP (cAMP), a key signaling molecule in the regulation of lipolysis.

The BFPCs in LEAN can enhance the breakdown of fat cells (lipolysis) by inhibiting PDE, an enzyme that typically slows down fat breakdown. PDE inhibition by BFPCs significantly affects overall metabolism, primarily through its impact on lipolysis and related metabolic processes. This mechanism leads to increased cyclic AMP (cAMP) levels within cells, particularly adipocytes, which act as a crucial second messenger in many cellular signaling pathways involved in energy metabolism (Aslam & Ladilov, 2022). The elevated cAMP levels trigger a cascade of events, including activating protein kinase A (PKA), which phosphorylates hormone-sensitive lipase (HSL) and perilipin, leading to enhanced lipolysis and increased fat mobilization. This process results in the breakdown of triglycerides into free fatty acids and

glycerol, which are released into the bloodstream and can be used as an energy source by various tissues. The increased availability of fatty acids can lead to enhanced fatty acid oxidation in tissues like muscle and liver, potentially contributing to an overall increase in metabolic rate. Additionally, cAMP signaling influences glucose metabolism in various tissues, promoting gluconeogenesis and glycogenolysis in the liver and potentially enhancing glucose uptake and utilization in muscle tissue.

The effects of PDE inhibition extend beyond direct metabolic processes, influencing adipokine production, thermogenesis in brown adipose tissue, insulin sensitivity, and potential appetite regulation (Yang, 2018). These combined effects may lead to long-term metabolic adaptations, including gene expression changes that could improve metabolic flexibility and efficiency. However, it is important to note that while these mechanisms are supported by a scientific understanding of cAMP signaling and metabolism, the specific extent and duration of these effects from BFPC supplementation would require further research, particularly in long-term human studies. This study provides evidence for the lipolytic effects of the BFPCs in LEAN on human fat cells through PDE inhibition.

LEAN Research Results

Research on the ingredients contained in LEAN has demonstrated significant clinical benefits leading to improvements in body composition, reduction of fat mass, improved ratio of lean muscle mass to fat mass, and better appetite control and discipline. A 12-week, randomized, double-blind, placebo-controlled trial of 86 overweight or obese Korean adults demonstrated significant benefits of the BFPCs in LEAN compared to a placebo for body composition, abdominal fat, blood biochemistry, and toxicity (Park et al., 2020). Dual-energy X-ray absorptiometry (DEXA) was used to assess the total body fat percentage and body fat mass

before and after the 12-week intervention. Computed tomography (CT) was used to assess visceral fat, subcutaneous fat, total abdominal fat, and visceral subcutaneous ratio. Bioelectrical impedance analysis was conducted to measure body fat mass, body fat percentage, and visceral fat area. Blood samples were assessed for lipid profile (total cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein cholesterol), fasting glucose, and high-sensitivity C-reactive protein. The study reported a significant reduction in body fat mass of 4.65% ($p = .030$) measured by DEXA, a significant decrease in body weight by 1.81% ($p = .002$), a significant reduction in BMI by 2.32% ($p = .002$), and a significant reduction in body fat percentage (-0.87 ± 2.07; $p = .007$) in the BFPC group compared to the placebo group (Park et al., 2020). Following 12 weeks of BFPC intervention, the waist circumference (-1.97– 3.81 cm; P= .001), the visceral fat area (-14.60–24.72cm2; P= .000), and total abdominal fat area (-22.64–51.10cm2; P= .005) as measured by CT were significantly changed. The research design had several strengths, including its randomized, double-blind, placebo-controlled nature, the use of advanced imaging techniques for body composition analysis, and a comprehensive assessment of both efficacy and safety. However, limitations were noted, such as the relatively short duration of 12 weeks, the specific focus on a Korean population (which may limit generalizability), and the modest sample size of 86 completers.

A study by E. Y. Jung et al. (2017) investigated the clinical benefits of a low dose of yeast protein hydrolysate on obesity and weight loss in 30 obese women over eight weeks. This randomized controlled trial divided participants into two groups: a control group and a group receiving 500 mg/day of yeast protein hydrolysate. The research aimed to determine if a lower dose of yeast protein hydrolysate could still produce significant anti-obesity effects. The results demonstrated significant weight, BMI, and body fat reductions in the yeast protein hydrolysate

group compared to the control group. Specifically, the yeast protein hydrolysate group experienced a decrease in fat mass from 25.9 kg at baseline to 23.8 kg at the end of the 8-week period ($P<0.01$) and a reduction in fat mass ratio from 38.8% to 36.5% ($P<0.05$). Additionally, the yeast protein hydrolysate group showed a significant reduction in calorie intake ($P<0.001$) and reported thinking about eating less often than the control group (Jung et al., 2017). The mechanism appears to be through calorie intake reduction, improved appetite control, and reduced sweet preference.

A study by Cases et al. (2015) investigated the effects of BFPCs in LEAN on body weight, abdominal fat, waist circumference, and muscle metabolism in overweight French men. A 12-week randomized, double-blind, parallel pilot trial assessed the efficacy of this citrus-based polyphenol extract in managing overweight and associated metabolic issues compared to a placebo in 25 overweight men ages 30-45 years with a BMI of between 26-29.9 kg/m^2. The study revealed significant improvements in body composition for the BFPC group, including reductions in body weight, abdominal fat, and waist circumference. Supplementation with BFPCs was associated with a significant decrease in body weight of 3.75%, of abdominal fat of 9.74%, a reduction in waist circumference of 7.50% and hip circumference of 5.33%, and, importantly, preservation of skeletal muscle mass during weight loss. Notably, the supplement appeared to help prevent skeletal muscle catabolism, suggesting a potential dual benefit of reducing body fat while preserving muscle mass (Cases et al., 2015). Additionally, the researchers observed significant improvements in metabolic parameters among participants taking BFPCs. While the research has several strengths, including its randomized, double-blind design and multiple outcome measures, limitations such as the small sample size and short duration were noted.

A randomized, controlled trial involving 54 obese adult participants investigated the effects of yeast protein hydrolysate on body weight and abdominal fat accumulation (Jung et al., 2014). The intervention consisted of administering yeast protein hydrolysate to men and women ages 20-50 years with a BMI ≥25 kg/m^2 for ten weeks, with the primary aim of assessing its impact on weight management and fat distribution using computed tomographic (CT) scans. CT scans are the gold standard for measuring abdominal fat mass. The study's key findings demonstrated that yeast protein hydrolysate supplementation can effectively reduce body weight in obese adults. Moreover, the research showed a notable reduction in abdominal fat accumulation among the participants. Regardless of gender, the yeast group showed a significant reduction in abdominal fat thickness after ten weeks of treatment (men -5.38 mm, women -4.48 mm) ($P < 0.001$), whereas the control group showed a slightly increased abdominal fat thickness (men 0.15 mm, women 2.17 mm). After ten weeks of treatment with yeast protein hydrolysate, the difference in the abdominal fat thickness between the control group (1.16 mm) and the yeast group (-4.93 mm) was significant ($P < 0.001$). A significant difference in the subcutaneous abdominal fat was also observed between the two groups after ten weeks of treatment (control, -1.77 cm^2 versus yeast, -16.71 cm^2; $P< 0.01$). In the control group, body weight increased by 0.83 kg versus a loss of 2.60 kg in the intervention group ($P < 0.001$). BMI increased in the control group by 0.29 kg/m2 compared to a 0.90 kg/m2 reduction in the intervention group ($P < 0.001$). These results are particularly significant because abdominal fat is associated with various health risks, including cardiovascular diseases and metabolic disorders. The study's focus on overall weight loss and specific reduction in abdominal fat provides a comprehensive view of the potential benefits of yeast hydrolysate supplementation.

A 12-week randomized, double-blind, placebo-controlled trial conducted by Dallas et al. (2014) evaluated the efficacy and safety of the BFPCs used in LEAN on weight management and metabolic parameters in healthy, overweight French individuals. The study involved 95 participants, 47 receiving the BFPCs and 48 receiving a placebo, administered twice daily with meals. The results showed significant improvements in body composition for the BFPC group compared to the placebo group. Waist circumference decreased by 5.71%, hip circumference by 4.71%, and abdominal fat by 9.73% in the BFPC group, with all differences being statistically significant ($p < 0.0001$). Additionally, the study found significant improvements in inflammatory markers and oxidative stress markers in the BFPC group, including reductions in C-reactive protein and fibrinogen, and positive changes in malondialdehyde, superoxide dismutase, and glutathione levels (Dallas et al., 2014). The study's strengths include its randomized, double-blind, placebo-controlled design and comprehensive assessment of body composition and metabolic parameters. However, limitations such as the relatively short duration and specific population of healthy overweight individuals were noted.

This study by Jung et al. (2011) investigated the weight reduction effects of a yeast protein hydrolysate with a molecular weight below 10 kDa on obese young women. The research involved 20 participants randomly assigned to either a placebo group (n=10) or a yeast protein hydrolysate group (n=10) receiving one g/day of the supplement. The intervention lasted for four weeks, focusing on assessing the potential of this yeast protein hydrolysate as a dietary supplement for weight management (Jung et al., 2011). The results demonstrated significant weight loss in the yeast protein hydrolysate group compared to the placebo group. The yeast protein hydrolysate group lost an average of 1.68 kg, while the placebo group lost 0.71 kg ($P < 0.05$). Additionally, the percent ideal body weight (PIBW) and body mass index (BMI) decreased

significantly in the yeast protein hydrolysate group (PIBW: 3.04%; BMI: 0.65 kg/m2) compared to the placebo group (PIBW: 1.26%; BMI: 0.27 kg/m2) (Jung et al., 2011). Although not statistically significant, the yeast protein hydrolysate group also showed slightly higher reductions in fat mass, percent body fat, body circumference, and skinfold thickness than the placebo group. This study is significant as it provides evidence for the potential of yeast protein hydrolysate as a natural supplement for weight management in obese young women. However, the study is limited by the relatively short duration and small sample size.

A study by Kim et al. (2004) investigated the effects of yeast protein hydrolysate on body fat reduction in dietary obese rats. The research utilized a rat model of dietary-induced obesity, where rats were fed a high-fat diet to induce an obese state. In the study design, the rats were divided into four groups of 8: low-fat diet (control), high-fat diet, high-fat diet with oral administration of yeast protein hydrolysate at 0.5g/kg of body weight, and high-fat diet with oral administration of yeast protein hydrolysate at 1.0g/kg of body weight. The key finding of the study was that yeast protein hydrolysate supplementation effectively reduced body fat and plasma triacylglycerol in obese rats (Kim et al., 2004). However, as an animal study, the results may not directly translate to human outcomes, and the specific mechanisms of action were not fully elucidated. Despite these limitations, this research demonstrated the potential of yeast hydrolysate in addressing dietary obesity, paving the way for future studies in this area. This was the first study on yeast protein hydrolysate investigating its potential as a weight management tool in combatting the obesity epidemic.

LEAN Safety, Toxicity, and Nutrikinetics

Jung et al. (2010) and colleagues evaluated the acute and subacute toxicity of yeast protein hydrolysate derived from Saccharomyces cerevisiae in Sprague-Dawley rats. The

research design included both acute and subacute toxicity tests. A single oral dose of 5,000 mg/kg of yeast protein hydrolysate was administered for the acute toxicity test, while the subacute toxicity test involved daily oral doses of 1,000 mg/kg for 14 days. Additionally, a satellite group was treated with the same dose for 14 days and observed for an additional 14 days after treatment cessation. The results of the study were consistently positive in terms of safety. In the acute toxicity test, no mortality or significant changes in general behavior were observed, and there were no significant changes in the gross appearance of internal organs. Similarly, the subacute toxicity test revealed no significant differences in organ weights between control and treated groups of both sexes. Hematological analysis and blood chemistry showed no toxic effects, and no gross abnormalities or histopathological changes were observed.

More recently, a comprehensive toxicity evaluation of the yeast protein hydrolysate used in LEAN was conducted in Sprague-Dawley rats to assess both acute and subacute oral toxicity (Ahn et al., 2021). In the acute toxicity test, the yeast protein hydrolysate was administered orally at a high dose of 5,000 mg/kg. The results showed no significant changes in body and organ weights compared to the control group. This indicates that yeast protein hydrolysate is well-tolerated even at high doses. For the subacute toxicity assessment, the yeast protein hydrolysate was administered orally at a dose of 1,000 mg/kg for 90 days. While some minor changes in hematological parameters were observed, they remained within normal ranges and were considered non-toxic. These findings suggest that the yeast protein hydrolysate used in LEAN is safe and non-toxic at both single high doses (5,000 mg/kg) and repeated doses (1,000 mg/kg) over an extended period. Interestingly, in the subacute toxicity study, a significant reduction in body weight was observed among male rats receiving the yeast protein hydrolysate.

A review by Muralidharan et al. (2023) investigated the nutrikinetics and urinary excretion of phenolic compounds after 16 weeks of supplementation with the flavanone-rich ingredient found in LEAN. The open-label trial involved 20 healthy overweight and obese volunteers divided into two dosage groups: a low dose (900 mg per day) and a high dose (1800 mg per day). Participants took the supplement in capsule form during breakfast and lunch and followed an individualized isocaloric diet, avoiding polyphenol-rich foods before and during pharmacokinetic measurements. Key findings from the study revealed that over 20 phase II and colonic metabolites were detected in plasma, with two peaks observed at 1 hour and 7-10 hours after the first capsule ingestion. No significant differences in Area Under the Curve (AUC) were found between the two doses for circulating metabolites. In urine, 53 metabolites were monitored, including human phase II and colonic metabolites. Cumulative urine excretion was higher with the high dose than the low dose in acute and chronic studies. Notably, total urinary metabolites were significantly lower at week 16 than in week 1. The study's significance lies in its contribution to understanding the long-term nutrikinetics and bioavailability of phenolic compounds from flavanone-rich supplements (Muralidharan et al., 2023). While the research has several strengths, including its long-term design and comprehensive analysis of metabolites, limitations such as the open-label design and small sample size were noted.

Conclusion

As the global prevalence of obesity continues to increase, the need for natural, safe, and effective weight control options becomes increasingly necessary. Make Wellness LEAN, and its combination of BPPs and BFPCs has emerged as a versatile and beneficial dietary supplement with a range of health-promoting effects, including lipid homeostasis, appetite control, enhanced lipolysis, lipid metabolism, and increased resting energy expenditure that helps optimize the

body compositions of humans. Its ability to support multiple mechanisms of action for supporting fat loss and metabolic health increases its effectiveness in reducing abdominal and subcutaneous fat while also reducing inflammation and oxidative stress and preserving muscle mass, which is crucial for long-term health and weight management. This research review contributes to the growing body of evidence supporting the use of natural compounds in addressing the global obesity epidemic. Additional longer-term studies utilizing the combination of BFPCs and BPPs in Make Wellness LEAN are needed to determine the synergies that exist with this formulation. These studies will further the understanding of the mechanisms responsible for the anti-obesity benefits of LEAN and elucidate the health benefits received by mitigating the adverse effects of obesity.

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