Research Article **Open Access**

FFHD
Functional Foods in Health and Disease

Effective body recomposition vs. misconceptions of the traditional weight loss strategies: TRCAP21 - a novel technological breakthrough in body recomposition

Debasis Bagchi[1,2*], Bernard W. Downs[2], Samudra P. Banik[3], Manashi Bagchi[4], Steve Kushner[5], Sanjoy Chakraborty[6], Bruce S. Morrison[7], Stephen Hesson[8]

[1]College of Pharmacy and Health Sciences, Texas Southern University, Houston, TX, USA; [2]Victory Nutrition International, Inc., Department of Research and Development, Bonita Springs, FL, USA;[3]Department of Microbiology, Maulana Azad College. Kolkata, India; [4]Dr. Herbs LLC, Concord, CA, USA; [5]ALM Research and Development, Oldsmar, FL, USA; [6]Department of Biological Sciences, New York City College of Technology/CUNY, Brooklyn, NY, USA; [7]Morrison Family and Sports Medicine, Huntingdon Valley, PA, USA; [8]PFHIX Inc., Neenah, WI, USA.

***Corresponding Author:** Debasis Bagchi, [1]College of Pharmacy and Health Sciences, Texas Southern University, Houston, TX, USA; [2]Victory Nutrition International, Inc., Department of Research and Development, Bonita Springs, FL, USA

Submission Date: February 18th, 2022; **Acceptance Date:** March 15th, 2022; **Publication Date:** April 1st, 2022

Please cite this article as: Bagchi D., Downs B.W., Banik S.P., Bagchi M., Kushner S., Chakraborty S., Morrison B.S., Hesson S. Effective Body Recomposition vs. Misconceptions of the Traditional Weight Loss Strategies: TRCAP21 - A Novel Technological Breakthrough in Body Recomposition. *Functional Foods in Health and Disease* 2022; 12(4): 134-150. DOI: https://www.doi.org/10.31989/ffhd.v12i3.905

ABSTRACT

Background: The prevalence of obesity has increased an astounding 30.5% to 42.2% over the last two decades despite numerous weight loss products and programs, thus qualifying it as an epidemic. Fat is the lightest of macromolecules, the highest energy reserve of the body, and the last reservoir of survival insurance to be expended. Water, muscle, and electrolytes are diminished prior to the expenditure of fat resources, the primary cause of rapid weight loss. Contrary to popular belief that only "weight gain" is the sole and correct parameter for evaluating healthy body recomposition, there are no less than 10 additional factors that contribute to a reduction in metabolic rate and an increase in fat storage. These are mostly ignored from considerations regarding the etiology of obesity. Our laboratory developed a novel formulation of D-ribose nicotinamide, alpha glycerol phosphorylcholine and four other evidence-based botanical constituents encapsulated in a Prodosomed stimulant- and sugar-free TRCAP21 (TrimRox™) formulation that effectively addresses those contributing factors. To investigate the feasibility of doing a 90-day randomized, double-blind placebo-controlled investigation, we conducted a 21-day concept validation pilot study on TRCAP21 in 9 subjects to assess changes in various body parts, including chest, upper arms, waist/belly, hips, and thighs, as well as body weight.

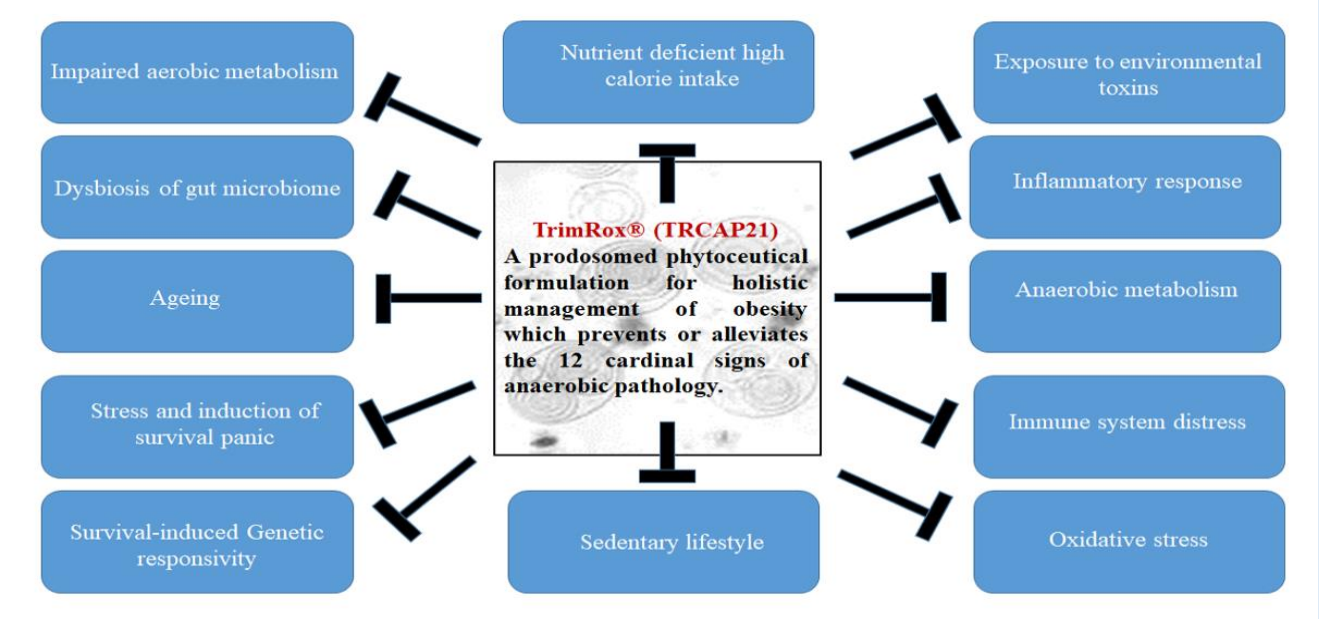
Objective: This physician-supervised 21-day concept validation pilot study on TRCAP21 was conducted on 9 subjects to determine changes in anthropometric parameters including chest, upper arms, waist/belly, hips, and thighs, as well as body weight, and determine the effect of TRCAP21 on energy, mood, satiety, and sugar cravings.

Materials and Methods: The study was conducted on nine male and female subjects (age: 47-70 years) to assess the efficacy of TrimRox™ over a period of 21 consecutive days. Body weights and anthropometric measurements were conducted at the initiation and termination of the study. The effect of TRCAP21 was evaluated on energy level, mood elevation, satiety level, sugar cravings, overall health, and adverse events in the subjects.

Results: The results demonstrated that all subjects experienced a reduction in size of one or more these body parts. In addition, it also led to significant improvements in mood elevation, satiety, reduced sugar cravings, elevated energy levels and overall mental and physical health. Intake of 1 packet twice a day (BID) before meals resulted in a significantly greater reduction of body measurements than consuming it once a day (OID). Surprisingly, body weight was reduced in all nine subjects from 2 lbs. to 11 lbs. The randomized double-blind placebo-controlled study is underway to confirm and further substantiate these findings.

Conclusion: The TRCAP21 Prodosomed nutraceutical formulation combines the evidence-based efficacy of 6 key constituents, mostly of botanical origin, that act synergistically to restore aerobic cellular metabolism, boost energy level, mood elevation, improve satiety, reduce sugar cravings, reduce body fat in various body compartments as well as weight and improve overall health. Owing to the encapsulation of the components in unique concentric layers of liposome, their release takes place in a sustained and sequential manner. It will be worthwhile to explore its effect on the Gut-Brain Axis, especially the associated microbiome in order to obtain further insights to more accurately define the multiple mechanisms of action.

Keywords: obesity, weight management, body recomposition, Aerobic body homeostasis, prodosome®, herbal nutraceuticals



INTRODUCTION

The prevalence of obesity in USA was 42.4% during 2017-2018, while that of severe obesity was 9.2% [1]. Interestingly, obesity prevalence was 40% in adults of age group 20-39 years, while obesity prevalence was 44.8% in age group between 40 to 59 years. However, there was a lower trend of 42.8% in adults over 60 years. Consequences of obesity are associated with a diverse number of diseases including type 2 diabetes, coronary heart disease (CHD), stroke, hypertension; gallbladder disease; breast, endometrial and colon cancers; osteoarthritis and premature death [2]. In USA, an

estimated annual medical cost of adult obesity ranges from $ 147 BN to nearly $ 210 BN [3]. Taken together, the obesity epidemic is alarmingly increasing at a skyrocketing pace in the USA.

In both medical and scientific communities, the most common terminologies are either "weight loss" or "weight management". However, a more focused and accurate indicator should specify changes in body composition, body size, or a reduction in fat mass instead of weight reduction only [4]. Specifically, "weight loss" is not at all a focused or reliable indicator as it specifically focuses on the heaviness of the body but doesn't reflect the healthy changes in body composition/size, or metabolic homeostasis [5]. Muscle mass, bone and body fluids are comparatively much heavier than fat, while fat is the lightest of macromolecules, and in the body recomposition process, fat is usually metabolized last to be eliminated from the body [5]. Thus, short-term expectations of weight loss from fat loss are erroneous.

Diverse factors such as hormonal balance, genetics and genetic predispositions, gut microbiota, neurotransmitters, and lifestyle have a major impact on energy metabolism, metabolic homeostasis, and fat metabolism [6]. Existing commercial weight loss strategies have greatly failed to achieve and maintain sustainable weight loss and enhance greater healthy fat loss.

MATERIALS AND METHODS

Study Protocol: This concept validation pilot study was supervised by Dr. Bruce S. Morrison, DO. All subjects were critically reviewed and included in this investigation. All subjects duly reviewed the detailed protocol and signed consent forms, which were endorsed by Dr. Morrison.

Study Subjects: The study was conducted in a total of nine volunteers [male = 3; female = 6; age = 47-70 Y] over a period of 21 consecutive days (Table 1). Adverse event monitoring was strictly enforced. All subjects maintained a daily diary and submitted it at the completion of the investigation.

Treatment Strategy: Eight subjects took a single dose of TrimRox™ 6.75 g per day in the morning in an empty stomach over a period of 21 consecutive days, while the ninth subject took two doses of 6.75 g per day, the first dose in an empty stomach in the AM and the second dose in an empty stomach in the afternoon, a total of 13.5 g per day, over a period of 21 consecutive days.

Anthropometric Measurements: **A**nthropometric measurements were conducted on changes in chest (inches), upper arm/bicep right and left (inches), hips (inches), thighs right and left (inches), and waist (inches) in addition to evaluating changes in body weights.

Behavioral Parameters: Effect of TRCAP21 on energy level, mood elevation, satiety level, sugar cravings, and overall health was regularly monitored over these 21 consecutive days of supplementation.

Adverse event monitoring: Adverse event monitoring was critically supervised. Daily diaries were critically checked and verified.

RESULTS:

Table 1 demonstrates the changes on diverse anthropometric parameters including changes in chest (inches), upper arm/bicep right and left (inches), hips (inches), thighs right and left (inches), and waist (inches) in these subjects following treatment with TrimRox™ over a period of 21 consecutive days. Modest reductions in all these parameters were observed (Table 1). Surprisingly, no increases were observed. In addition, body weight reduced in all nine subjects from 2 lbs. to 11 lbs. Table 2 demonstrates the effect of TRCAP21 on energy level, mood elevation, satiety level, sugar cravings, and overall health over these 21 consecutive days of supplementation.

No adverse events were reported.

Table 1. Effect of TRCAP21 on multiple anthropometric parameters as well as body weight in male and female subjects

Gender (Age)	Dose (g)	Anthropometric Measurements																
		Chest (Inches)		Upper Arm/Bicep (Inches)				Hips (Inches)		Thighs (Inches)				Waist/Belly (Inches)		Body Weight (lbs)		
		Initial	Final	Right		Left				Right		Left						
				Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Δ Change
F (55)	6.75	41.25	40.5	13.5	13.5	13	13	44.5	44.5	26.5	26	26.25	25.75	44.5	44.25	178	176	-2.0
F (62)	6.75	42	41	13	12.5	13	12.5	43.5	43	23.5	22	23.5	22	41	40	178	175	-3.0
F (47)	6.75	49	48	15	13.25	13	12.75	47.5	47	25.5	24.75	24.5	24	43	41.5	208	197	-11.0
M (54)	6.75	50.5	49.5	14	14	13.75	14	46	45.5	23	22	22.75	21.5	52.5	50	280	272	-8.0
M (54)	6.75	43	43	14.5	14	14.5	14	44	41	23	24	23	24	41	40	214	210	-4.0
F (70)	6.75	46.5	45.5	16	15	16	15.5	51	49.75	27.25	26.5	27.25	26.5	50.75	48.5	229	224	-5.0
F (65)	6.75	43.5	42	13.75	13.75	14	13.5	49	47.5	26.25	26.25	25.5	25.25	49.5	48.5	173	167	-6.0
F (54)	6.75	45	42	12.75	11.75	12	11	41	40	24	24	24.5	23.5	40.5	38	176	170.5	-5.5
M (55)*	13.5	53.5	51	16	15	15.5	14.5	52	50.5	26	24	26.5	23.5	56.5	53.5	306	300	-6.0

*An employee of VNI Inc, Bonita Springs, FL; M= Male; F = Female

Table 2. Effect of TRCAP21 on energy, mood, satiety, and sugar cravings in subjects

	Gender (Age)	Dose (g)	Energy Level	Mood Improvement	Satiety Level	Sugar Cravings	Sleep	Overall Health	Adverse Events
1	F (55 Y)	6.75	**+++**	+++	+++	Reduced sugar cravings	+++	Improved	None
2	F (62 Y)	6.75	**++**	+++	+++	Reduced sugar cravings	+++	Improved	None
3	F (47 Y)	6.75	**++**	NR	+++	No Effect	+++	Improved	None
4	M (54 Y)	6.75	**+++**	NR	+++	NR	NR	Improved	None
5	M (54 Y)	6.75	**+++**	+++	+++	Reduced sugar cravings	+++	Improved	None
6	F (70 Y)	6.75	**++**	+++	+++	Reduced sugar cravings	+++	Improved	None
7	F (65 Y)	6.75	**++**	NR	+++	Reduced sugar cravings	NR	Improved	None
8	F (54 Y)	6.75	**+++**	+++	+++	Reduced sugar cravings	+++	Improved	None
9	M (55 Y)*	13.50	**+++**	NR	+++	Reduced sugar cravings	NR	Improved	None

*An employee of VNI Inc, Bonita Springs, FL; M= Male; F = Female; NR = None reported

Key: + = modest improvement; ++ = better improvement; +++ = significantly better improvement

Overall, this 21-day concept validation pilot study demonstrates that TRCAP21 enhanced healthy body recomposition observed as a reduction in size of various body parts, increased energy levels, elevated mood, enhanced satiety, reduced sugar cravings, improved restful sleep, and improved overall health. Interestingly, consistent, but varying amounts of weight loss were observed, although, Crawford et al. [7] have reported earlier that a healthy and effective body recomposition strategy can result in a small net gain in weight due to an increase in exercise-induced muscle density, while resulting in a loss of size and improvements in healthy body recomposition. Subjects in the study made no other changes to their lifestyle.

Cascade of Events: Overindulgence of healthy/unhealthy foods, sedentary lifestyle and lack of exercise are the critical factors leading to overweight and obesity. However, there are additional significant contributory factors not addressed by conventional weight loss/management products and programs. It is essential to have a decent lifestyle with a regular, healthy, nutritious, and balanced diet with limited amounts of alcoholic beverages, poultry, fish and red meat,

moderate amount of exercise, and restful sleep to maintain good health. Implementation of a healthy lifestyle in conjunction with TrimRox™ (TRCAP21) Prodosomed nutraceutical technology will contribute to obtaining a healthy improvement in body composition with reduced fat and water storage, improved muscularity, and even some weight loss.

Obesity is associated with several lifestyle factors including (i) genetics, (ii) poor, unhealthy, and sedentary lifestyle, (iii) chronic stress, (iv) toxic environmental exposure, and (v) disruption in energy homeostasis. Furthermore, chronic stress, trauma, infection, and allergen/antigen insults induce tissue hypoxia or hypoxic/anaerobic events leading to a massive inflammatory response and survival panic [8].

TrimRox™ (TRCAP21) Prodosomed nutraceutical formulation effectively and discretely addresses the salient features, as outlined in Table 1, involved in obesity. The basis or prime objective of this formulation was to restore aerobic metabolic cellular homeostasis to optimize oxygen utilization and hydration status, mitigate oxidative stress, and improve body composition parameters, i.e., promote body recomposition [9-11].

DISCUSSION

Obesity is thus often related directly to the lack of sufficient physical activity, lack of energy homeostasis, and poor dietary habits. However, a lot of other intrinsic and extrinsic factors also play an equally pertinent role in regulating predisposition to excess fat accumulation. A major cause of obesity is metabolic dysfunction leading to a loss of physiological homeostasis, enhanced dependence on anaerobic pathways, accumulation of ROS, and elicitation of inflammatory responses, all culminating in a significant increase in survival-induced energy conservation; a decline in the basal/resting metabolic rate and the rate of lipid oxidation; and increased fat storage [5,6].

Energy Homeostasis: Three discrete forms of survival insurance are genetically preprogrammed in a human body which includes (a) Fat, (b) Sugar as glycogen, and (c) water. An upregulation of these survival insurance storage components takes place when the body is placed in a "survival panic" mode along with a retardation in energy expenditure [12,13]. As stated elsewhere, chronic degenerative disorders are induced by anaerobic pathologies and in turn cause genetically triggered survival panic. As stated earlier, several intricate factors induce the incidence of obesity and metabolic syndrome. Following are the causative factors that play a regulatory role in the pathophysiology of obesity:

(a) Overindulgence of high-fat, carbohydrate-filled nutrient-deficient junk foods.
(b) Lack of physical activity and sedentary lifestyle.
(c) Continued exposure to structurally diverse environmental pollutants, toxic chemicals, fertilizers, fungicides, insecticides, herbicides, toxic heavy metals, antibiotics, pigments, and colorants.
(d) Compromised digestive health, gut dysbiosis, inflammatory bowel disorders (IBD), and hyperacidity.
(e) Enhanced anaerobic metabolism.
(f) Increased inflammatory response leading to an increase in insulin resistance and enhanced fat accumulation around the belly.
(g) Increased fat storage.
(h) Compromised and increased energy conservation.

(i) Increased oxidative stress and oxidative DNA damage.

(j) Compromised immune system

(k) Chronic stress, impaired cognition, depression, and elevated sadness.

(l) Advancing age and premature aging.

(m) Impaired aerobic homeostasis, enhancing anaerobic glycolysis and compromising metabolic homeostasis, leading to deficiency in circulating AMPK; all of these contribute to energy disruption, abdominal (and other body compartments) fat deposition and storage.

Of these 13 vital parameters, the "weight management" industries are basically targeting only the first two prime factors of overindulgence of unhealthy foods, and sedentary lifestyle/lack of exercise.

Selected strategies may help in enhancing fat metabolism. These include: (i) minimize sugar, gluten, and fast-food consumption, (ii) improve healthy lifestyle, nutritious balanced diet, and moderate exercise, and (iii) consumption of appropriate research-driven dietary supplements. All of these can optimize energy production, maximize cellular metabolism, and the removal of cellular wastes leading to a more desirable body composition, enhanced lean body mass, healthy muscle mass and optimal health.

It is quite evident that conventional weight loss strategies/techniques completely failed to appropriately address the biological, genetic, and metabolic consequences that occur with advancing age. Several factors are critically important to control the obesity epidemic including: (i) optimize hormonal levels, (ii) minimize anaerobic pathologies caused by cellular oxygen deprivation, (iii) optimize metabolic homeostasis and enhance fat metabolism/oxidation, (iv) optimize cardiovascular, gastrointestinal, neuromuscular, and kidney health, and (v) promote healthy gut microbiome.

Detrimental effect of anaerobic pathologies on fat metabolism: A broad spectrum of anaerobic pathologies has been demonstrated to induce an inability to effectively utilize oxygen leading to an increased anaerobic metabolism and lactate accumulation [9]. A disruption in oxidative pathologies, in conjunction with increased lactate production, led to an upsurge in H+ increasing cellular acid burden with a reduction in blood pH leading to progressive acidemia. All these will induce a metabolic transition towards cellular anaerobic glycolysis, and a compensatory expenditure of alkalinizing histidine molecules from the heme protein of deconjugated hemoglobin (Hb), which in turn releases iron. These cause an upsurge of anaerobic/acidic cellular events, which cause a series of pathological manifestations including a perturbation of fat metabolism, inflammatory sequela, compromised cardiovascular function, and vaso-occlusive incidences [10].

Influence of inflammatory response on fat metabolism: Chronic inflammatory conditions exert an array of anaerobic sequela including a disruption in the glucose-insulin system, upregulation of white adipose tissue, and macrophage-associated inflammatory sequela, all of which lead to obesity [11].

Enhanced production of oxygen free radicals, oxidative injury, and fat metabolism: An increase in anaerobic metabolic events causes an upsurge of oxidative stress,

inflammatory sequela, and adipose tissue hypoxia that further induces an array of anaerobic pathologies including mitochondrial dysfunctions, development of type 2 diabetes mellitus, adipose hypertrophy, and a massive disruption in energy homeostasis [11-13]. Therefore, an inability to effectively utilize cellular oxygen (i.e., ↑anaerobic metabolism) increases the production of ROS and enhances fat storage.

Immune distress and its impact on fat metabolism: An array of inflammatory sequela play an instrumental role in enhanced fibrosis, angiogenesis, altered lipid metabolism including lipids, cholesterol, and fatty acids; and immune cell activation and immune distress [14-15].

Influence of stress on fat metabolism: Increased stress induces significant stress on cells, potentially impairing cellular oxygen utilization, and exerting massive demands on cells. This cascade of events induces an increase in hunger and appetite for high-fat, sweet, and salty foods [16].

Effect of unpropitious gene expression of hormones and neurotransmitters on fat metabolism Leptin: Research studies have demonstrated that increased obesity, T1D, T2D, infertility, and Rabson-Mendenhall Syndrome can occur because of leptin resistance or deficiency [17-18]. Energy homeostasis, hunger/appetite, metabolism, endocrine functions, and fat storage in adipocytes are regulated by leptin, a 167 amino acid adipocytokine. Appropriate regulation of leptin will potentially decrease fat storage in adipocytes and provide significant benefits in the regulation of obesity, body weight, and metabolic syndrome, as well as improve reproductive health, hematopoiesis, blood pressure, hypertension, lymphoid organ homeostasis, bone density and bone mass [17-18].

Ghrelin (Hunger hormone): Under the influence of excessive stress and sufficient physiological disruption, anaerobic/hypoxic metabolic events are induced that trigger a state of genetically mediated “survival panic”. This then increases energy conservation and ultimately potentiates hunger signaling [19-20]. A conventional corrective strategy includes regulating/inhibiting ghrelin release and enhancing leptin release [19-20], to restore aerobic metabolism and terminate “survival panic” signaling.

Reproductive hormones: The hypothalamus is a key component that regulates energy homeostasis, specifically energy intake and energy expenditure [21]. An injury in the hypothalamus causes a perturbation in energy homeostasis. The hypothalamus is equipped with two nuclear estrogen receptor (ER) proteins, viz. ERα and Erβ, which regulate food intake and body weight. For example, as an activation of ERα reduces food intake, body weight, and meal size, as well as promotes synthesis of AMPK and adipose tissue triglyceride lipase (ATGL)-mediated lipolysis providing free fatty acids as a fuel to activate UCP-1. These estrogen receptors are available in multiple peripheral tissues including adipose tissue [22-23]. The availability of estrogens in the adipose tissue causes anti-inflammatory activities in the peripheral tissues and in the central nervous system, which prevents women from experiencing multiple inflammatory consequences. Thus, some additional estrogen may provide a therapeutic benefit in regulating obesity and anti-inflammatory efficacy [22-24].

Thyroid hormones and neurotransmitters: Two major hormones including triiodothyronine (T3) and tetraiodothyronine (thyroxine or T4) are produced and released by the thyroid gland, which are important for (i) metabolic homeostasis, (ii) cardiac functions, (iii) digestive functions, (iv) muscle control, (v) neuronal development and function, and (v) bone function. The third active thyroid hormone, 3,5-Diiodothyronine (3,5-T_2) or just T2, stimulate the TRb receptor of thyroid hormones that controls energy expenditure [25-28].

Two prime neurotransmitters: serotonin and dopamine: It has been extensively demonstrated that an interruption/dysfunction in feeding signals by neuronal cells plays a vital role in obesity. Neurotransmitters are basically chemical messengers that transmit signals to multiple target cells including different neurons, muscle cells, or gland cells [29]. Serotonin is specifically involved in the transmission of nerve impulses and plays a major role in appetite control/suppression [29-30].

Deficiency of dopamine in obese individual can be easily characterized by increased food intake and food consumption behaviors [31]. Dopamine not only regulates food cravings, but also motivation and reward circuitry.

Consequential effects of premature aging on fat metabolism: An upsurge in oxidative stress, increased cellular lactic acid production, and anaerobic glycolysis are pioneering hallmarks of impaired cellular metabolism. All these events lead to chronic degenerative disorders/disease including accelerated premature aging and, are classic pathophysiological characteristics of anaerobic/hypoxic events. Thus, restoring aerobic glycolysis must be an important anti-aging objective to reduce the anaerobic cellular metabolic requirement that induces a concomitant increase in anaerobic-induced lactic acid production [32].

Accordingly, we hypothesize that the Prodosomed TRCAP21 phytoceutical technology should minimize anaerobic-based metabolic impairments and combat a full spectrum of etiological obesogenic factors.

Role of AMPK (adenosine monophosphate-activated kinase) on fat metabolism: AMPK is a key enzyme known to regulate cellular energy balance. However, it declines with advancing age. AMPK enhances fat oxidation and energy production (ATP), however, a decline in AMPK enhances the conversion of sugar into fat along with a concomitant increase in fat storage [33-36]. Thus, in a successful body recomposition strategy, rejuvenating AMPK synthesis and metabolism should be a most important objective.

A synergistic botanical formulation - TRCAP21: This novel formulation was designed using the following Prodosomed six research-affirmed nutraceutical ingredients (Figure 1).

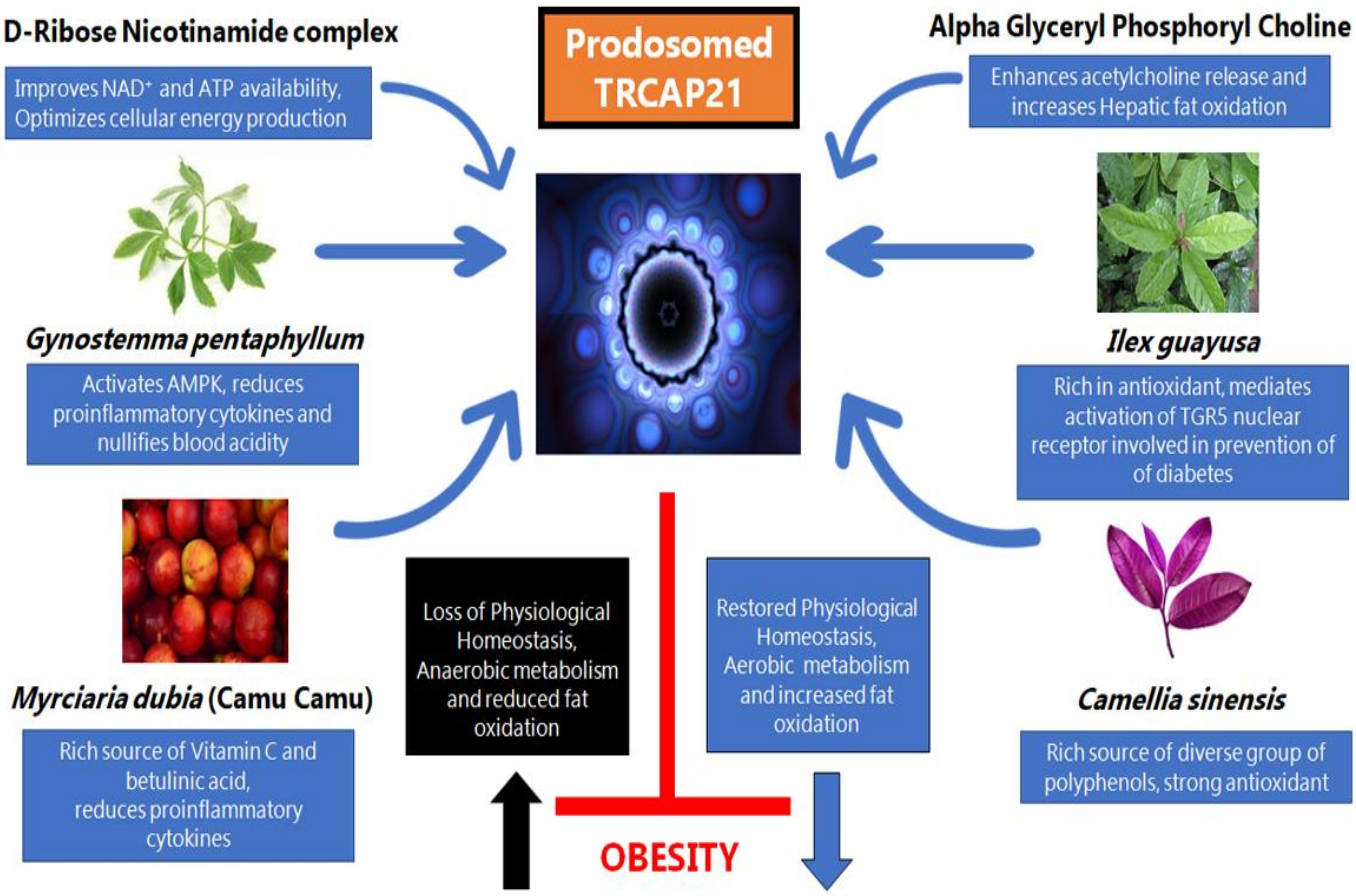


Fig 1. Prodosomed TRCAP21 as a novel anti-obesity formulation: A major cause of obesity is metabolic dysregulation and dysfunction leading to loss of physiological homeostasis, enhanced dependence on anaerobic pathways, accumulation of Reactive Oxygen Species and elicitation of inflammatory response, all culminating in a significant decline in the rate of lipid oxidation. Prodosomed TRCAP21 is a proprietary formulation consisting of extracts of six vital plant derived constituents that collectively ensure restoration of normal physiological homeostasis thus mitigating obesogenic factors. Abbreviations: NAD+ - Nicotinamide Adenine Dinucleotide, ATP – Adenosine Triphosphate, AMPK - Adenine Mono Phosphate activated Protein Kinase, TGR5 – Takeda G Protein Coupled Receptor/G-Protein Coupled Bile Acid Receptor

D-Ribose nicotinamide complex (RiaGev; Source: Bioenergy): In a clinical investigation, a proprietary blend of D-ribose and nicotinamide exhibited enhanced bioavailability and effectively promoted the synthesis of nicotinamide adenine dinucleotide (NAD)[37]. A pilot study in one human volunteer demonstrated that blood NAD+ can elevate up to 2.7-fold following the administration of a single dose of RiaGev. A pharmacokinetic study in twelve human volunteers demonstrated that administration of a single dose of 100, 300 and 1,000 mg of RiaGev can enhance blood NAD+ metabolome significantly [38]. It is important to mention that maximum concentration of NAD, a coenzyme in redox reactions and a donor of ADP-ribose moieties in ADP-ribosylation reactions, is in the mitochondria and is important to optimize cellular energy production. The safety and efficacy of RiaGev was also investigated in 18 subjects (age = 35-65 years) in a single-center, randomized, double-blind, comparator controlled, cross-over study. Interestingly, both ATP and ADP levels increased by approximately 7.3%, while both NAD+ and NADP+ levels increased by approximately 15%, and

glutathione level (GSH) increased by 11% and maintained redox homeostasis. Improvements in muscle and brain performance were observed along with GSH. Furthermore, increases in insulin response and glucose tolerance were also observed along with a steady reduction in salivary cortisol. Quality of life, attention, focus, and motivation levels improved significantly as well. In conclusion, RiaGev provides effective benefits to all tissues as well as a synergistic dose-response was observed between RiaGev and NAD metabolites in the liver, muscle, and brain tissues [39].

***Gynostemma pentaphyllum* (GP) leaf extract:** This leaf extract activates and increases AMPK level, which is instrumental in regulating cellular energy balance. It also enhances fat oxidation, energy production, and glucose homeostasis; and inhibits cholesterol synthesis [~~38,40~~ 34,36]. In cellular mitochondria, AMPK activation enhances conversion of ingested food molecules into ATP. Moreover, it upregulates catabolic pathways through glycolysis and fatty acid oxidation to boost energy homeostasis (ATP) [33-36].

GP also reduces cytokine production and activates NF-κB and STAT3 signaling in lipopolysaccharide-induced macrophages, without affecting their viability [40]. GP extract has been reported to exhibit multiple beneficial effects including maintenance of healthy cholesterol and blood glucose levels; increasing hemoglobin, liver glycogen, and muscle glycogen concentrations; decreasing blood lactic acid (BLA) levels and blood urea nitrogen (BUN) concentrations; boosting immunity; and protecting cells from mutations [41-44]. Park et al. [45] conducted a randomized, double-blind, placebo-controlled clinical investigation in 80 obese subjects (age: 40.08 ± 10.60 years; weight: 74.58 ± 9.19 kg; BMI: 27.53 ± 1.22 kg m^{-2}) using a GP extract (450 mg/day) over a period of 12 consecutive weeks. Body weight, body fat mass, percent body fat, and BMI were significantly decreased in the treatment group. No adverse events were observed [45].

***Myrciaria dubia* (JS0208 Camu Camu) whole-berry extract (MD):** Camu Camu is a potent antioxidant containing considerable amounts of vitamin C, betulinic acid, beta-carotene, riboflavin, thiamine, niacin, cyanidin 3-glucoside, delphinidin 3-glucoside, ellagic acid, kaempferol, myricetin, quercetin, quercitrin, rutin, and micronutrients. It protects genomic DNA integrity, enhances energy level and immune competence, and exhibits anti-inflammatory benefits by downregulating cytokine production and c-reactive proteins (CRP), and suppresses water retention (inhibits edema formation). It also facilitates tissue reconstruction and repair and provides protection against allergens and mutagens [46-49].

***Ilex guayusa* Loes. (Family Aquifoliaceae) (Guayusa) leaf extract (GL)**: GL leaf extract contains potent structurally diverse antioxidants and phytonutrients including chlorogenic acid, ursolic acid, as well as caffeine [50,51]. Especially, ursolic acid exerts a pronounced mechanistic role in the activation of nuclear receptor TGR5, which in turn is instrumental in the management of metabolic syndrome by enhancing energy expenditure and insulin sensitization [51-53].

In a battery of safety studies, GL leaf extract demonstrated broad spectrum safety with no genotoxicity, and secured FDA-notified GRAS (Generally Recognized as Safe) status in 2019 [54].

GL leaf extract has been demonstrated to elevate mood and enhance cognition and focus, promote brain function, restful sleep, alleviate stress, promote cardiovascular health, antiviral potential against herpes simplex virus, and protect against potential neurotoxins and hepatoxicity [55].

It was observed that the action of Guayusa caffeine source distinctly differs from other natural and synthetic caffeine sources as it did not induce a significant effect on epinephrine (adrenaline). This can explain its reduced adrenaline-related side effects compared to other caffeine sources. Also, no significant effect of Guayusa was observed on dopamine, norepinephrine, or GABA levels [56].

Purple Tea (PT; HS1222 Camellia sinensis extract; PurpleForce™): This "purple" variation of *Camellia sinensis* extract was derived from plants grown in a high-altitude mountain area exposed to strong UV rays, which increase the protective properties of the plants. PT has high polyphenol content including delphinidin content and exerts higher antioxidant activity compared to other tea extracts [57].

PT exhibits diverse beneficial antioxidant and anti-inflammatory effects including: (i) improves nitric oxide production, (ii) restores blood flow, (ii) improves recovery from exercise-induced muscular injury by decreasing creatine kinase, oxidative injury, and exercise-induced soreness, (iii) and promotes exercise recovery [58]. In a clinical study, PT exhibited a significant reduction in body weight, BMI, abdominal fat, triglycerides in serum and hepatic tissues; and suppression of fat absorption, increasing hepatic fat metabolism, and enhanced expression of carnitine palmitoyl transferase (CPT) 1A [59]. Another study assessed the efficacy of supplemental PT (100 mg/day) in 30 healthy exercising men after strenuous and stressful exercise over a period of 8 consecutive days [59]. Muscle endurance performance was remarkably improved and lactate dehydrogenase level, a marker of muscular injury, was significantly reduced. Overall, these results strengthen the pronounced role of PT in human health and well-being.

Alpha Glyceryl phosphoryl choline (Alpha-GPC; AlphaSize®-): The cholinergic system is the largest neurotransmitter system in the body regulating brain-to-muscle communication, intestinal peristalsis, and locomotion; attention, higher-order cognitive processing, and emotions [60-62]. Alpha-GPC is a safe, non-stimulating endurance-enhancing ergogenic supplement, and exhibited to improve memory, focus, learning, cognition, mood, and physiological performance in athletes [62]. Following administration of Alpha-GPC, choline and growth hormone secretion, and hepatic fat oxidation significantly increased. Alpha-GPC was shown to boost endurance and performance, while preventing the reduction of choline levels [63-64].

The Prodosomed TRCAP21 is a proprietary formulation (Figure 1) comprised of D-ribose nicotinamide, alpha-GPC and four botanical extracts rich in a diverse range of phytoceutical components, including

phytosaccharides, theobromine, (and other dimethylxanthines viz. paraxanthine and theophylline), amino acids, gallic acid, guanidine, isobutyric acid, B-vitamins, vitamin C, nitric oxide, chlorogenic acid, ellagic acid, triterpenes and pentacyclic triterpenoid acids, saponins (such as gypenosides), and alcohols, including ursolic acid (0.7–1%) and amyrin esters (up to 0.5%), betulinic acid; bioactive phenolic compounds including anthocyanins (cyanidin-3-O-glucoside and delphinidin-3-O-glucoside), flavonols (myricetin, quercetin), ellagic acid, ellagitannins, proanthocyanidins, and carotenoids (lutein, carotene, violaxanthin and luteoxanthin), etc., that collectively act to mitigate obesogenic factors and restore aerobic metabolism and normal physiological homeostasis [65].

Overall, this unique and proprietary TRCAP21 formulation technology exerted significant benefits and improvement in overall body composition in these nine volunteers as evident from the reduced anthropometric measurements of the chest, bicep, hips, thighs, and waist, as well as modest, varying, but noteworthy reductions in body weight. Energy levels, mood, and restful sleep were improved. Moreover, reduced appetite or appetite correction was reported by all subjects, and sugar cravings were also reduced. Overall health improved and no adverse events were reported.

This pilot concept validation study motivated us to do a full-fledged IRB (Institutional Review Board)-approved randomized, double-blind, placebo-controlled study, with clinicaltrials.gov approval (#NCT05283525), which is now in progress.

CONCLUSION

It has been difficult for any therapeutics/food supplements/nutraceuticals to make significant headway into the management of obesity owing to human being's general insufficient physical activity and inherent craving for sweet, salty, fatty, tasty, and fried junk foods. As incidences of obesity and associated ailments continue to rise even faster, the need of the hour is to explore more unique and effective natural remedies instead of synthetic ones and use them in correct synergistic proportions to plan anti-obesity regimens and achieve a healthy and balanced lifestyle. Since the management of obesity also depends to a significant extent on the mental health and wellness of the affected person, it will be worthwhile to investigate the effect of the constituents of TrimRox™ over the communication network of the Gut-Brain Axis [66], particularly on the associated microbiome to understand how nutraceuticals influence the complex human-microbe associations for ensuring optimal body homeostasis, both mentally as well as physically.

List of Abbreviations: ACh: Acetylcholine; ADP: Adenosine diphosphate; Alpha-GPC: Alpha Glyceryl phosphoryl choline; ATGL: Adipose tissue triglyceride lipase; AMPK: Adenosine monophosphate-activated kinase; ATP: Adenosine triphosphate; BID: Twice a day BMI: Body mass index; BN: Billion; CHD: Coronary heart disease; CNS: Central nervous system; CPT: Carnitine palmitoyl transferase; CRP: C-Reactive protein; DNA: Deoxyribonucleic acid; ER: Estrogen receptor; FDA: Food and Drug Administration; GABA: Gamma amino butyric acid; GHG: 1,2-Di-O-galloyl-4,6-O-(S)-hexahydroxy-diphenoyl-β-D-glucose; GL: Guayusa (Ilex guayusa Loes.) leaves; GP: *Gynostemma pentaphyllum*; GRAS: Generally recognized as safe; GSH: Glutathione; Hb: Hemoglobin; IBD: Inflammatory bowel disease; IRB: Institutional review board; MD: *Myrciaria dubia* (also known as Camu Camu); NAD+: Nicotinamide adenine dinucleotide+; NADH: Nicotinamide adenine dinucleotide (NAD) + hydrogen (H); OID: Once a day; PT: Purple tea; ROS:

Reactive oxygen species; T1D: Type 1 diabetes mellitus; T2 or 3,5-T2z; 3,5-Diiodothyronine; T2D: Type 2 diabetes mellitus; T3: Triiodothyronine; T4 or thyroxine: Tetraiodothyronine; UCP-1: Uncoupling protein-1

Authors' Contribution: DB, BD, SK, MB, SB, and SC significantly contributed to designing and drafting the manuscript. Dr. Bruce Morrison was intricately associated with the clinical investigation and data analyses. SH standardized the ingredients and cooperated in designing the formulation.

Competing Interests: Commercial Division of Victory Nutrition International (VNI), Inc., Bonita Springs, FL, USA, is involved in marketing this product. BD is an employee of Research and Development Division of VNI Inc., Bonita Springs, FL, USA. DB, SK, and MB are scientific consultants. BM is an independent physician. SH is an ingredient designers and manufacture

Acknowledgment: The authors thank Ms. Kim Downs for her generous assistance towards the completion of the manuscript.

Funding: Bioscience Division of Victory Nutrition International, Inc., Bonita Springs, FL, USA.

REFERENCES

1. Adult Obesity Facts: Obesity is a common, serous, and Costly disease. Feb 11, 2021. https://www.cdc.gov/obesity/data/adult.html. Retrieved Feb 28, 2022.
2. Wolf AM, Colditz GA. Current Estimates of the Economic Cost of Obesity in the United States. *Obesity Research,* 1998; 6(2): 97-106. https://doi.org/10.1002/j.1550-8528.1998.tb00322.x.
3. Strategies to Overcome and Prevent Obesity Alliance. Obesity School of Public Health and Health Services. 2021. The George Washington University. https://stop.publichealth.gwu.edu/sites/stop.publichealth.gwu.edu/files/documents/Fast%20Facts%20Cost%20of%20Obesity.pdf. Retrieved Feb 11, 2022.
4. World Health Organization (WHO): Obesity and Overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Retrieved Feb 21, 2022.
5. Managing overweight and obesity in adults; Systematic evidence review from the obesity expert panel, 2013. US Dept of Health and Human Services, NIH; https://www.nhlbi.nih.gov/health-topics/managing-overweight-obesity-in-adults. Retrieved Feb 11, 2022.
6. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. 2009. Annual Medical Spending Attributable to Obesity: Payer-And Service-Specific Estimates. Health Affairs; Vol 28: Supplement 1 https://www.healthaffairs.org/doi/10.1377/hlthaff.28.5.w822. Retrieved Feb 26, 2021.
7. Crawford V, Scheckenbach R, Preuss HG. Effects of niacin-bound chromium supplementation on body composition in overweight African-American women. *Diabetes, Obesity and Metabolism,* 1999; 1(6): 331-337. https://doi.org/10.1046/j.1463-1326.1999.00055.x.
8. Downs BW, Corbier JR, Speight N, Kushner S, Aloisio T, Bagchi M, Bagchi D. Anemia: Influence of Dietary Fat, Sugar, and Salt on Hemoglobin and Blood Health. In: Dietary Sugar, Salt, and Fat in Human Health. Editors: Preuss HG, Bagchi D eds. (2020) Boston (MA): Elsevier/ Academic Press, pp. 103-128.
9. Baillie-Hamilton PF. Chemical Toxins: A Hypothesis to Explain the Global Obesity Epidemic. *The Journal of Alternative and Complementary Medicine,* 2002; 8(2): 185-192. https://doi.org/10.1089/107555302317371479.
10. Hyman MA. Environmental toxins, obesity, and diabetes: An emerging risk factor. *Alternative Therapy in Health and Medicine,* 2010; 16(2): 56-58. PMID: 20232619
11. Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients,* 2012; 4(8): 1095–1119. https://doi.org/10.3390/nu4081095.
12. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. 2016. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Medicine,* 2016; 8:42 https://doi.org/10.1186/s13073-016-0303-2.
13. Phypers B, Pierce T. Lactate physiology in health and disease. *Continuing Education in Anesthesia and Critical Care and Pain,* 2006; 6(3): 128–132. https://doi.org/10.1093/bjaceaccp/mkl018.
14. Corbier JR, Downs BW, Kushner S, Aloisio T, Bagchi D, Bagchi M. VMP35 MNC, a novel iron-free supplement, enhances cytoprotection against anemia in human subjects: a novel

hypothesis. *Food and Nutrition Research,* 2019; 63: 3410 https://doi.org/10.29219/fnr.v63.3410.

15. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *Journal of Clinical Investigation,* 2003; 112(12): 1821-1830. https://doi.org/10.1172/JCI19451
16. Netzer N, Gatterer H, Faulhaber M, Burtscher M, Pramsohler S, Pesta D. Hypoxia, oxidative stress and fat. *Biomolecules,* 2015; 5(2); 1143-1150 https://doi.org/10.3390/biom5021143
17. Zhang Y, Chua S Jr. Leptin function and regulation. *Comprehensive Physiology,* 2017; 8(1): 351-369. https://doi.org/10.1002/cphy.c160041.
18. Triantafyllou GA, Paschou SA, Mantzoros CS. Leptin and hormones: energy homeostasis. *Endocrinology and Metabolism Clinics of North America*, 2016; 45(3): 633-645. https://doi.org/10.1016/j.ecl.2016.04.012.
19. Akki R, Raghay K, Errami M. Potentiality of ghrelin as antioxidant and protective agent. *Redox Report,* 2021; 26(1):71–79. https://doi.org/10.1080/13510002.2021.1913374.
20. Downs BW, Bagchi M, Morrison BS, Galvin J, Kushner S, Bagchi D. PerformLyte – A Prodosomed PL425 PEC Phytoceutical-Enriched Electrolyte Supplement – Supports Nutrient Repletion, Healthy Blood pH, Neuromuscular Synergy, Cellular and Metabolic Homeostasis. In: Antioxidants and Functional Foods for Neurodegenerative Disorders: Uses in Prevention and Therapy. Editors: Kumar A, Bagchi D (2021) Boca Raton (FL): CRC Press/ Taylor & Francis, pp. 399-424.
21. Leeners B, Geary N, Tobler PN, Asarian L. Ovarian hormones and obesity. *Human Reproduction Update,* 2017; 23(3): 300-321. https://doi.org/10.1093/humupd/dmw045.
22. Lainez NM, Coss D. Obesity, Neuroinflammation, and Reproductive Function. *Endocrinology,* 2010; 160(11): 2719-2736. https://doi.org/10.1210/en.2019-00487.
23. Santollo J, Wiley MD, Eckel LA. Acute activation of ER alpha decreases food intake, meal size, and body weight in ovariectomized rats. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, 2007; 293(6):R2194-201. https://doi.org/10.1152/ajpregu.00385.2007.
24. Santos RS, Frank AP, Fatima LA, Palmer BF, Oz OK, Clegg DJ. Activation of estrogen receptor alpha induces beiging of adipocytes. *Molecular Metabolism,* 2018; 18: 51–59. https://doi.org/10.1016/j.molmet.2018.09.002.
25. Brown LM, Gent L, Davis K, Clegg DJ. Metabolic impact of sex hormones on obesity. *Brain Research,* 2010; 1350: 77-85. https://doi.org/10.1016/j.brainres.2010.04.056.
26. Goglia F. The effects of 3,5-diiodothyronine on energy balance. *Frontiers in Physiology*, 2014; 5:528. https://doi.org/10.3389/fphys.2014.00528.
27. Lombardi A, Senese R, De Matteis R, Busiello RA, Cioffi F, Goglia F, Lanni A. 2015. 3,5-Diiodo-L-thyronine activates brown adipose tissue thermogenesis in hypothyroid rats. *PLOS ONE*, 2015; 10 (2): e0116498. Bibcode:2015PLoS One.1016498L https://doi.org/10.1371/journal.pone.0116498.
28. Jonas W, Lietzow J, Wohlgemuth F, Hoefig CS, Wiedmer P, Schweizer U, Köhrle J, Schürmann A. 3,5-Diiodo-L-thyronine (3,5-T2) exerts thyromimetic effects on hypothalamus-pituitary-thyroid axis, body composition, and energy metabolism in male diet-induced obese mice. *Journal of Endocrinology*, 2015; 156(1): 389–99. https://doi.org/10.1210/en.2014-1604.
29. Miller GD. Appetite Regulation: Hormones, Peptides, and Neurotransmitters and Their Role in Obesity. *American Journal of Lifestyle Medicine,* 2019; 13(6): 586–601. https://doi.org/10.1177/1559827617716376.
30. Blum K, Febo M, Badgaiyan RD. 2016. Fifty Years in the Development of a Glutaminergic-Dopaminergic Optimization Complex (KB220) to Balance Brain Reward Circuitry in Reward Deficiency Syndrome: A Pictorial. *Austin Addiction Science,* 2016; 1(2): 1006. PMCID: PMC5103643. NIHMSID: NIHMS822953. PMID: 27840857.
31. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler FS. Brain dopamine and obesity. *Lancet,* 2001; 357(9253): 354-357. https://doi.org/10.1016/s0140-6736(00)03643-6.
32. Chung KW. Advances in understanding of the role of lipid metabolism in aging. *Cells,* 2021; 10: 880. https://doi.org/10.3390/cells10040880.
33. Carling D. The AMP-activated protein kinase cascade—a unifying system for energy control. *Trends in biochemical sciences,* 2004; 29(1): 18-24. https://doi.org/10.1016/j.tibs.2003.11.005.
34. Fogarty S, Hardie DG. Development of protein kinase activators: AMPK as a target in metabolic disorders and cancer. *Biochimica Biophysica Acta*, 2010; 1804(3): 581-591. https://doi.org/10.1016/j.bbapap.2009.09.012.
35. Hardie DG. AMPK: a key regulator of energy balance in the single cell and the whole organism. *International Journal of*

Obesity (London), 2008; 32 (Suppl 4): S7-S12. https://doi.org/10.1038/ijo.2008.116.

36. Zhang BB, Zhou G, Li C. AMPK: an emerging drug target for diabetes and the metabolic syndrome. *Cell Metabolism,* 2009; 9(5): 407-416. https://doi.org/10.1016/j.cmet.2009.03.012.
37. Trammell SAJ, Schmidt MS, Weidemann BJ, Redpath P, Jaksch F, Dellinger RW, Li Z, Abel ED, Migaud ME, Benner C. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nature Communications,* 2016; 7:12948; 1-14. https://doi.org/10.1038/ncomms12948.
38. Hopp AK, Grüter P, Michael O, Hottiger MO. Regulation of Glucose Metabolism by NAD+ and ADP-Ribosylation. *Cells,* 2019; 8(8): 890. https://doi.org/10.3390/cells8080890.
39. Dölle C, Rack JGM, Ziegler M. NAD and ADP-ribose metabolism in mitochondria. FEBS J., 2013; 280(15): 3530-3541. https://doi.org/10.1111/febs.12304.
40. Wong WY, Lee MLL, Chan BD, Ma VWS, Zhang W, Yip TTC, Wong WT, Tai WCS. Gynostemma pentaphyllum saponins attenuate inflammation in vitro and in vivo by inhibition of NF-κB and STAT3 signaling. *Oncotarget,* 2017; 8(50): 87401–87414. https://doi.org/10.18632/oncotarget.20997.
41. Megalli S, Davies NM, Roufogalis BD. Anti-hyperlipidemic and hypoglycemic effects of Gynostemma pentaphyllum in the Zucker fatty rat. *Journal of Pharmacy and Pharmaceutical Sciences,* 2006; 9(3): 281-291. PMID: 17207412
42. Yeo J, Kang YJ, Jeon SM, Jung UJ, Lee MK, Song H, Choi MS. Potential hypoglycemic effect of an ethanol extract of Gynostemma pentaphyllum in C57BL/KsJ-db/db mice. *Journal of Medical Foods,* 2008; 11(4): 709-716. https://doi.org/10.1089/jmf.2007.0148
43. Lu HF, Chen YS, Yang JS, Chen JC, Lu KW, Chiu TH, Liu KC, Yeh CC, Chen GW, Lin HJ, Chung JG. Gypenosides induced G0/G1 arrest via inhibition of cyclin E and induction of apoptosis via activation of caspases-3 and 29 in human lung cancer A-549 cells. *In Vivo,* 2008; 22(2): 215-221. PMID: 18468406
44. Razmovski-Naumovski V, Huang THW, Tran VH, Li GQ, Duke CC, Roufogalis BD. Chemistry and pharmacology of Gynostemma pentaphyllum. *Phytochemistry Reviews,* 2005; 4: 197-219. https://doi.org/10.1007/s11101-005-3754-4
45. Park SH, Huh TL, Kim SY, Oh MR, Pichiah T, Chae SW, Cha YS. Antiobesity effect of Gynostemma pentaphyllum extract (Actiponin): A randomized, double-blind, placebo-controlled trial. *Obesity,* 2014; 22(1): 63-71. https://doi.org/10.1002/oby.20539.
46. Langley PC, Pergolizzi JV Jr, Taylor R Jr, Ridgway C. Antioxidant and associated capacities of Camu camu (Myrciaria dubia): a systematic review. Journal of Alternative and Complementary Medicine, 2015; 21(1): 8-14. https://doi.org/10.1089/acm.2014.0130.
47. Fracassetti D, Costa C, Moulay L, Tomás-Barberán FA. Ellagic acid derivatives, ellagitannins, proanthocyanidins and other phenolics, vitamin C and antioxidant capacity of two powder products from camu-camu fruit (Myrciaria dubia). Food Chemistry, 2013; 139(1-4): 578-588. https://doi.org/10.1016/j.foodchem.2013.01.121.
48. Yazawa K, Suga K, Honma A, Shirosaki M, Koyama T. Anti-inflammatory effects of seeds of the tropical fruit camu-camu (Myciaria dubia). Journal of Nutritional Science and Vitaminology (Tokyo), 2011; 57(1): 104-107. https://doi.org/10.3177/jnsv.57.104.
49. Inoue T, Komoda H, Uchida T, Node T. Tropical fruit camu-camu (Myrciaria dubia) has anti-oxidative and anti-inflammatory properties; A randomized controlled trial. Journal of Cardiology, 2008; 52(2):127-132. https://doi.org/10.1016/j.jjcc.2008.06.004.
50. Dueñas JF, Jarrett C, Cummins I, Logan–Hines E. Amazonian guayusa (Ilex guayusa Loes.): A historical and ethnobotanical overview. *Economic Botany,* 2016; 70: 85–91. https://ayusa.com.au/wp-content/uploads/Duenas_etal2016.pdf
51. García-Ruiz A, Baenas N, Benítez-González AM, Stinco CM, Meléndez-Martínez AJ, Moreno DA, Rualesa J. Guayusa (Ilex guayusa L.) new tea: Phenolic and carotenoid composition and antioxidant capacity. *J Sci Food Agric*., 2017; 97(12): 3929–3936. https://doi.org/10.1002/jsfa.8255.
52. Brinckmann J, Brendler T. Herb Profile: Guayusa (Ilex guayusa family: Aquifoliaceae). *Herbalgram* 2019; 6: Issue 124. https://www.herbalgram.org/resources/herbalgram/issues/124/table-of-contents/hg124-herbprofile-guayusa/.
53. Chianesea G, Golin-Pachecob SD, Taglialatela-Scafatia O, Colladoc JA, Munoz E, Appendino G, Pollastro F. Bioactive triterpenoids from the caffeine-rich plants guayusa and mate'. *Food Research International,* 2019; 115: 504–510. https://doi.org/10.1016/j.foodres.2018.10.005.
54. GRAS Notice (GRN) No. 835 from the Food Additive Safety. https://www.fda.gov/food/generally-recognized-safe-gras/gras-notice-inventory (Retrieved Feb 8, 2022).
55. Gamboa F, Muñoz CC, Numpaque G, Sequeda-Castañeda LG, Gutierrez SJ, Ellez N. Antimicrobial Activity of Piper marginatum Jacq and Ilex guayusa Loes on Microorganisms Associated with Periodontal Disease. *International Journal*

of Microbiology, 2018; Article ID 4147383: 9 pages https://doi.org/10.1155/2018/4147383 .

56. Kreiger DR, Kalman DS, Feldman S, Arnillas L, Goldberg D, Gisbert O, Nader S. The safety, pharmacokinetics, and nervous system effects of two natural sources of caffeine in healthy adult males. *Clinical and Translational Science*. 2016; 9(5): 246–251. https://doi.org/10.1111/cts.12403
57. Cesareo K, Ziegenfuss T, Raub B, Sandrock J, Lopez H. Effects of Purple tea on muscle hyperemia and oxygenation, serum markers of nitric oxide production and muscle damage, and exercise performance. *Journal of Exercise and Nutrition,* 2020; 3(3): 13 ISSN 2640-2572. https://www.journalofexerciseandnutrition.com/index.php/JEN/article/view/71
58. Harty PS, Zabriskie HA, Erickson JL, Molling PE, Kerksick CM, Jagim AR. Multi-ingredient pre-workout supplements, safety implications, and performance outcomes: a brief review. *Journal of International Society of Sports Nutrition,* 2018; 15(1):41. https://doi.org/10.1186/s12970-018-0247-6.
59. Shimoda H, Hitoe S, Nakamura S, Matsuda H. Purple tea and its extract suppress diet-induced fat accumulation in mice and human subjects by inhibiting fat absorption and enhancing hepatic carnitine palmitoyl transferase expression. *International Journal of Biomedical Sciences,* 2015; 11(2): 67-75. PMCID: PMC4502735 PMID: 26199579.
60. Teipel SJ, Meindell T. Grinberg L, Grothe M, Cantero JL, Reiser MF, Moller HJ, Heinsen H, Hempel H. The cholinergic system in mild cognitive impairment and Alzheimer's disease: An in vivo MRI and DTI study. *Hum Brain Mapp*., 2011; 32(9): 1349–1362. https://doi.org/10.1002/hbm.21111.
61. Avila DS, Gubert P, Roos DH, Puntel R, Aschner M. Manganese: Encyclopedia of Food and Health. Editors: Caballero B, Finglas PM, Toldra F (2016) Boston (MA): Elsevier/ Academic Press, pp. 637-640.
62. Parnetti L, Abate G, Bartorelli L, Cucinotta D, Cuzzupoli M, Maggioni M, Villardita C, Senin U. Multicentre study of l-alpha-glyceryl-phosphorylcholine vs ST200 among patients with probable senile dementia of Alzheimer's type. *Drugs Aging,* 1993; 3(2): 159-164 https://doi.org/10.2165/00002512-199303020-00006.
63. Kawamura, T, Okubo T, Sato K, Fujita S, Goto K, Hamaoka T, Iemitsu M. 2012. Glycerophosphocholine enhances growth hormone secretion and fat oxidation in young adults; a clinical trial. *Nutrition,* 2012; 28(11-12):1122-1126. https://doi.org/10.1016/j.nut.2012.02.011.
64. Ziegenfuss T, Landis J, Hofheins J. Acute supplementation with alpha-glycerylphosphorylcholine augments growth hormone response to, and peak force production during resistance exercise. *Journal of International Society of Sports Nutrition,* 2008; 5(Suppl 1): P15 https://doi.org/10.1186/1550-2783-5-S1-P15.
65. Bondia-Pons I, Ryan L, Martinez JA. Oxidative stress and inflammation interactions in human obesity. *Journal of Physiology and Biochemistry,* 2012; 68: 701–711. https://doi.org/10.1007/s13105-012-0154-2 .
66. Appleton J. The gut-brain axis: Influence of microbiota on mood and mental health. *Integrative Med. (Encinitas)*, 2018; 17(4): 28–32. PMCID: PMC6469458 PMID: 31043907