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Comparison of NutriFusion Supplements with Synthetic Vitamins

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Abstract

Nutraceuticals are essential food constituents that provide nutritional benefits as well as medicinal effects. The benefits of these foods are due to the presence of active compounds such as carotenoids, collagen hydrolysate, and dietary fibers. Nutraceuticals have been found to positively affect cardiovascular and immune system health and have a role in infection and cancer prevention. Nutraceuticals can be categorized into different classes based on their nature and mode of action. Synthetic vitamins are a booming industry, but their benefits are limited due to the general nature of the chemicals. **Hypothesis:** In this study, we compared different synthetic vitamins to nutraceuticals (GrandFusion, GF) and their potential therapeutic activity. **Methods:** Daily administration of GF diets (2%) compared to a one a day vitamin over a period of 4-months in C57BL6 mice increased mitochondrial DNA and general mitochondrial enzyme activity and enhanced mitochondrial mRNA synthesis compared to synthetic vitamin supplementation. Compared to the synthetic vitamins, all GF diets augmented mRNA expression of mitochondrial biogenesis constituents, including peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), mitochondrial transcription factor A (Tfam), estrogen-related receptor alpha (ERRα), nuclear respiratory factor 1 (NRF-1), cytochrome c oxidase IV (COXIV) and ATP synthase (ATPsyn). **Key findings:** Mice treated with GF diets showed an increase in running behavioral parameters when compared to control and synthetic vitamin treated mice. GF diets enhanced protein expression of cell signaling elements including AMP-activated

protein kinase (AMPK), sirtuin 1 (SIRT1), PGC-1*α* and peroxisome proliferator-activated receptor gamma (PPAR-g), compared to synthetic vitamins. Finally, GF diets reduced autophagy and the expression of phosphorylated ribosomal protein S6 kinase 1 (p-S6K1). **Conclusions:** These results suggest that GF diets are more effective in improving baseline metabolic pathways compared to synthetic vitamins.

Keywords

Diet, Inflammation, Behavior, Vitamins, Minerals

1. Introduction

Though they may claim to serve the same principles, functional foods *look like food*, while dietary supplements seem drug-like and can induce drug-like effects in high enough concentrations [1]. Under the aegis of "dietary supplements," nutraceuticals are any whole food—not an isolated nutrient or vitamin—that is concentrated and repackaged in a non-food format like a capsule or as a powder [2]. Many synthetic vitamins lack the essential elements like transporters and co-factors that are associated with naturally occurring vitamins [3] [4]. According to the Organic Consumers Association (OCA) and the Federal Drug Association (FDA), synthetic vitamins are not used or recognized by the body in the same way as the natural products [5] [6]. Natural vitamins come in packages with other vitamins, enzymes and minerals that control the way the body recognizes, metabolizes and uses them to make what it needs [7].

Synthetic vitamins do not always provide what we are expecting from their use [8] [9]. The synthetic version of Vitamin E is often referred to as the DL-form [10]. The DL-form is a combination of the D-form (which is the naturally occurring form) and the L-form (which usually does not occur in nature) [11]. Under many conditions, the L-form is not metabolized and utilized by the body and is excreted [12]. This pertains mainly to vitamins and not to amino acids or sugars, which are effectively consumed by the body. Synthetic forms of fat-soluble vitamins can be especially dangerous because they can build up in fatty tissues and cause toxicity [13]. The reason that the synthetic forms are more dangerous is because high concentrations are obtained through vitamin supplementation compared to the amounts that are attained from food-based forms [14].

GrandFusion® (GF) is a nutraceutical mixture of fruits and vegetables, that are enriched in "natural" vitamins and minerals that can attenuate neurological disorders like stroke, Alzheimer's disease and traumatic brain injury [15]-[17]. Additionally, GF extracts have been shown to enhance memory and learning in elderly rats by altering antioxidant enzymes and signaling pathways [18]. Previous studies have shown that GF diets can exert anti-inflammatory, antioxidant, neuroprotective and neurogenic properties [19] [20].

In the current study, we inquired about the influence of GF diets enriched in vegetables and fruits verses synthetic vitamins on the physiological and biochemical benefits in mice. Mice were fed GF diets enriched in fruits and vegetables or synthetic materials for 20 weeks and then examined. The results divulged that natural diets-maintained performance in several different behavioral assays by altering metabolic functions while the synthetic vitamins had little to no effect. We have established that the supplemented GF diets improved mitochondrial biogenesis and augmented functional consequences through the activation of AMPK, SIRT1, PGC-1a and PPARg. These results imply that diets supplemented in natural vitamins and nutrients can impact the general functional aspects of life.

2. Materials and Methods

2.1. Animal Experiments

C57BL/6J mice (10-weeks old, Jackson Laboratories, Bar Harbor, ME, USA) were kept at 25˚C ± 2˚C, with 55% ± 5% relative humidity under a 12-h light/12-h dark cycle in the animal facility at the University of South Florida (USF). Mice (60 mice) were divided into three groups (using a random generator): Group 1 was fed a normal chow diet (Con,); Group 2 was fed a 2% GrandFusion (GF1, NF-216—Fruit and Veggie #1 Blend), with the normal chow; Group 3 was fed a 2% GrandFusion diet (GF2, NF-316—Fruit #2 Blend) with normal chow; Group 4 was fed a 2% GrandFusion diet (GF3, NF-316—Vegetable #3 Blend) with normal chow; Group 5 was fed a 2% GrandFusion diet (GF4, NF-661—12-Fruit & Vegetable Blend) with normal chow; and Group 6 was fed an equivalent diet of One-A-Day Multi-vitamin blend (listed on last page)with normal chow (Syn) make available by NutriFusion, LLC (Naples, FL, USA) https://nutrifusion.com/ described previously [15]-[17]. After 20 weeks of oral supplementation, the endurance paradigm for the mice was quantified before the mice were euthanized. This study adhered to the Guide for the Care and Use of Laboratory Animals and was approved. Animals were randomly assigned to the different groups and were evaluated by investigators blinded to the studies. No animals were excluded from studies.

2.2. Endurance Testing

Grip strength was determined from all four limbs using a grip strength meter (San Diego Instruments, San Diego, CA, USA). To measure the grip strength force, mice were removed from their home cage, gripping the base of the tail between the thumb and forefinger. For forelimb measurement, the mouse was lowered over the grid keeping the torso horizontal and allowing only its forepaws to attach to the grid before and measurements were taken. The mouse was gently pulled back by its tail ensuring the mouse gripped the top portion of the grid and the torso remained horizontal and recorded the maximal grip strength value. Forelimb and hindlimb measurement, the mouse was lowered over the grip keeping the torso parallel with the grid and allowing both its forepaws and hindpaws to attach to the grid before any measurements were taken. Measurements were re-

peated three times, and the data were averaged. A mouse treadmill was used to determine the running distance (Omnitech Electronics, Inc., Columbus, OH, USA) [21] [22]. Mice were allowed to run on the treadmill until they were spent. The treadmill was set at a 10% incline, and the speed was 18 cm/s at the beginning and was increased by 3 cm/s every 2 min, following 3 days of acclimation running at 18 cm/s for 5 min. For fine motor coordination and stamina, the mice were arranged on an accelerating rotarod (San Diego Instruments, San Diego, CA) and the rod was slowly accelerated and latency to fall was recorded.

2.3. Reverse Transcription-Polymerase Chain Reaction

RNA was isolated from the soleus muscle with TRIzol reagent (ThermoFisher-Invitrogen, Carlsbad, CA, USA) and converted to cDNA (ThermoFisher-Applied Biosystems, Waltham, MA, USA). mRNA expression was quantified, the cDNA was amplified (ThermoFisher-Applied Biosystems, Waltham, MA, USA). PCR reactions were carried out and the PCR products were detected by gel electrophoresis and visualized. b-Actin was used as an internal control. The primers were as follows: PGC-1a—Forward GTCCTTCCTCCATGCCTGAC, Reverse GACTGCGGTTGTGTATGGGA; ERRa—Forward GAGGTGGACCCTTTGCCTTT, Reverse GGCTAACACCCTATGCTGGG; NRF-1—Forward CTTCATGGAGGAGCACGGAG, Reverse ATGAGGCCGTTTCCGTTTCT; Tfam—Forward GAGCGTGCTAAAAGCACTGG, Reverse CCACAGGGCTGCAATTTTCC; COXIV—Forward GGGCCTCGTTAGTGCAGCAGG, Reverse GGGCTCCCAGAAAAGGTTGCCT; ATPsyn—Forward TGGGGACCAGGGCAGCCATT, Reverse AGGGCTTGCTGCCCACACAT; b-Actin—Forward GCTCCGGCATGTGCAA, Reverse AGGATCTTCATGAGGTAGT.

2.4. Western Blot Analysis

Tissues were prepared using RIPA lysis buffer (Boston Bioscience, Boston, MA, USA) with the addition of a protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO, USA). The protein lysates concentrations were determined. The primary antibodies used were phosphor-AMPK, AMPK, SIRT1, b-actin (1:1000; Cell Signaling, Beverly, MA, USA), PGC-1a, PPARg, phosphor-S6K1 and S6K1 (1:1000; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA). Bound antibodies were detected using horseradish peroxidase-linked secondary antibodies (1:5000; Molecular Probes/Invitrogen, Eugene, OR, USA) for 2 h. Proteins were detected with chemiluminescence and visualized using the DigiDoc-it Imaging System (UVP, Upland, CA, USA). b-actin was used as an internal control.

2.5. Examination of Mitochondrial Content and Enzyme Activity in Muscle

Tissue samples were collected at the end of the study. Mitochondria were isolated by a density gradient centrifugation (ThermoFisher, Waltham, MA, USA). Samples were homogenized in mitochondria isolation buffer and mitochondria were

isolated [23]. Activity of cytochrome *c* oxidase (COX) was quantified by mixing isolated mitochondria and ferrocytochrome *c*, and absorption at 550 nm was measured to determine COX activity of the samples (Invitrogen, Camarillo, CA, USA). Activity of b-hydroxyacyl-CoA dehydrogenase (b-HAD) was determined [23]. The activity of citrate synthase (CS) was measured (Sigma-Aldrich, St. Louis, MO).

2.6. Analysis of Mitochondrial DNA Content

RNA was collected from tissue using TRIzol reagent (Invitrogen, Eugene, OR, USA) and translated to cDNA. The ratio of mtDNA and genomic DNA was determined by measuring relative density of the band. The following primers (IDT, Coralville, WA, USA) were used: mtDNA-specific 16s rRNA, forward CCGCAAGGGAAAGATGAAAGAC, reverse TCGTTTGGTTTCGGGGTTTC, and nuclear genome-specific hexokinase 2 gene, forward GCCAGCCTCTCCTGATTTTAGTGT, reverse GGGAACACAAAAGACCTCTTCTGG.

2.7. Statistical Analysis

The data was communicated as the mean ± standard deviation (SD). The statistical significance of the outcomes in the different studies was evaluated using a T-test or one-way analysis of variance (ANOVA) with Tukey's post hoc test. ANOVA was used for repeated measures and the significance of the difference between groups was evaluated by Tukey's post hoc test.

EXPERIMENTAL DESIGN

Diets

The mice were randomly divided into three groups:

Group 1 received a normal chow diet (Con)

Group 2 received a 2% GrandFusion (GF1, NF-216 - Fruit and Veggie #1 Blend), with the normal chow

Group 3 received a 2% GrandFusion diet (GF2, NF-316 - Fruit #2 Blend) with normal chow

Group 4 received a 2% GrandFusion diet (GF3, NF-316 - Vegetable #3 Blend) with normal chow

Group 5 received a 2% GrandFusion diet (GF4, NF-661 - 12-Fruit & Vegetable Blend) with normal chow

Group 6 received an equivalent diet of One-A-Day Multi-vitamin blend with normal chow (Syn)

Provided by NutriFusion, LLC (Naples, FL, USA) https://nutrifusion.com/ described previously [15]-[20].

3. Results

3.1. Diets, Food Intake and Weight

Mice were provided diets supplemented with GrandFusion diets or synthetic vitamins (2%) for 20 weeks. The 2% diet was used based on previous studies [15]-

[20]. The groups were as follows: Group 1 received the normal diet; Group 2 received a 2% GrandFusion (GF1, NF-216—Fruit and Veggie #1 Blend), with the normal diet; and Group 3 received a 2% GrandFusion diet (GF2, NF-316—Fruit #2 Blend) with the normal diet; Group 4 received a 2% GrandFusion diet (GF3, NF-316—Vegetable #3 Blend) with normal chow; Group 5 received a 2% GrandFusion diet (GF4, NF-661—12-Fruit & Vegetable Blend) with normal chow; and Group 6 received an equivalent diet of One-A-Day Multi-vitamin blend with normal chow (Syn).

The diets were similar to those used in previous studies [15]-[17]. The animals were monitored for food intake and body weight every week for the entire study. **Figure 1(A)** demonstrates a constant intake of food over the course of the study by all groups. The mice showed similar weight gains over the time of the experiment.

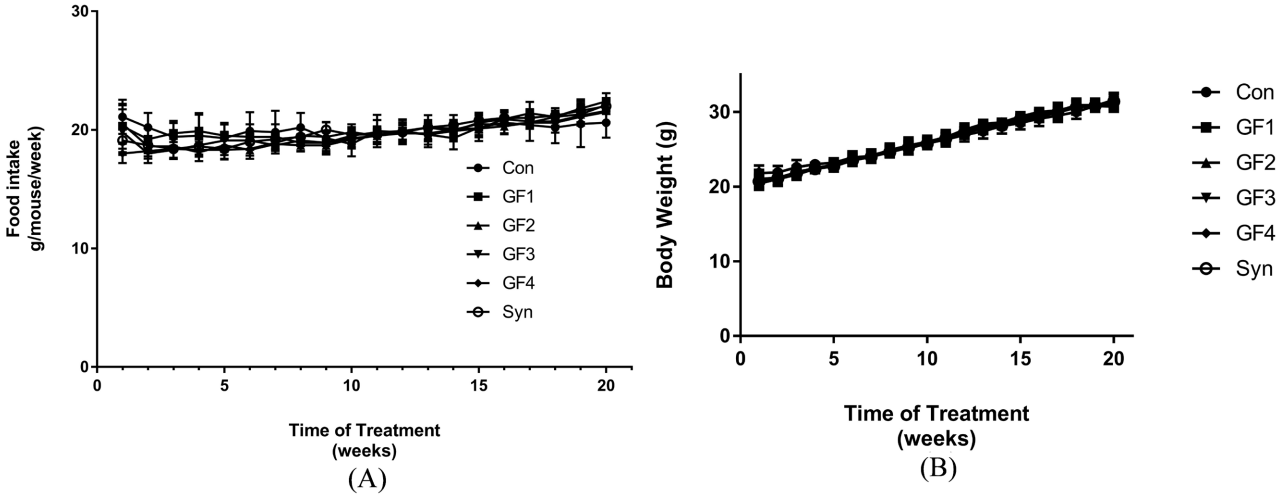

Figure 1. GF and Synthetic diets on food intake and body weight. (A) Changes in food intake during 20 weeks of treatment; (B) Changes in body weight in mice on various diets over 20 weeks. Mice were fed a normal diet or diets supplemented with 2% GF or synthetic vitamins. Each point represents mean +/− SD (n = 10 per group).

3.2. Exercise and Endurance

To understand the influence of diets on activity and eventually exercise endurance, the animals were exposed to different protocols (**Figure 2**). Mice on the GF1, GF2, GF3 and GF4 diets displayed a 150% increase in total distance in contrast to the mice on the control (**Figure 2(A)**). The mice on the GF diets showed a 165% and 172% increase in the treadmill time (**Figure 2(B)**). When the GF mice were exposed to a rotarod, there was a 120% increase in the time to fall when compared to the control diet (**Figure 2(C)**). When the GF diets were compared to the control and synthetic diets for grip strength, there was at least a 140% increase on the GF diets (**Figure 2(D)**). In addition, there was a significant increase in exercise endurance in mice on the GF diets compared to the control and synthetic diet animals with at 131% and 153% increase in both the soleus (SM) and gastrocnemius (GM) muscles weights (respectively, **Figure 2(E)**).

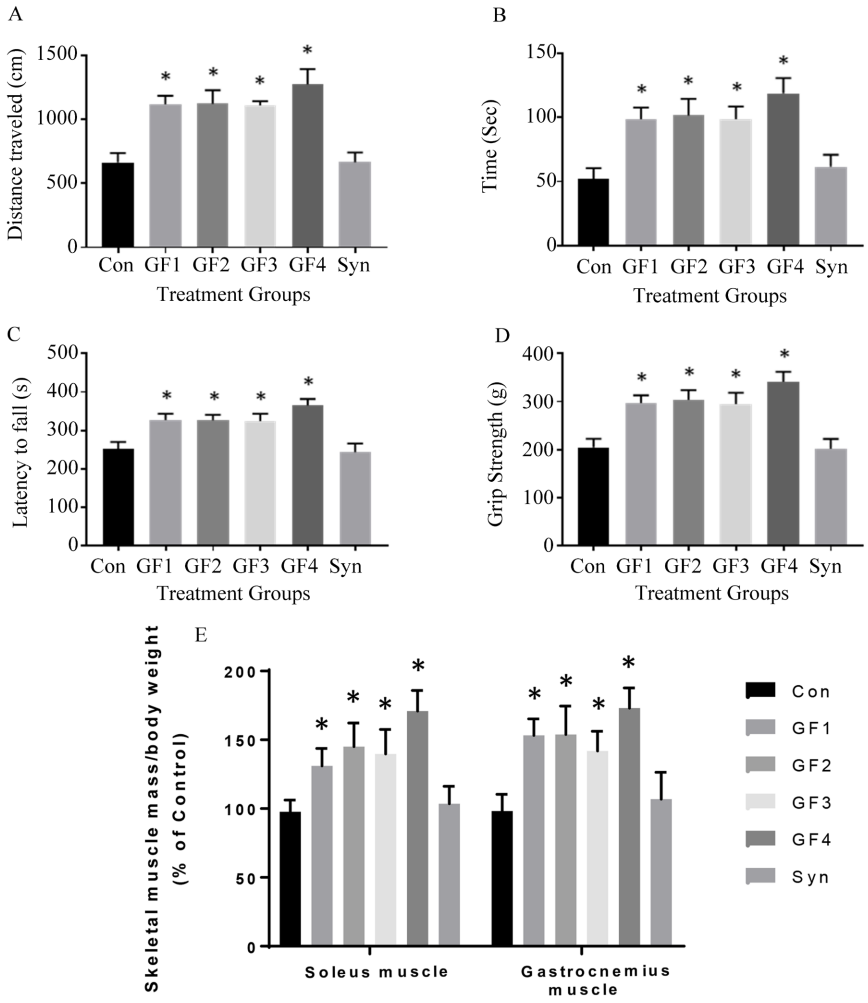

Figure 2. Effects of GF and Syn diets on exercise endurance and skeletal muscle mass in mice. (A) Distance and (B) Time of control mice and mice fed a normal diet enriched with GF or Syn supplements; (C) Fall time in a rotarod test; (D) grip strength; and (E) the ratio of skeletal muscle mass (soleus and gastrocnemius muscle)/body weight in normal, GF and Syn supplemented mice. Data are expressed as the mean +/− SD (n = 10 per group, *P < 0.01 compared to control group.

3.3. Impact on Mitochondrial Function

The impact of the GF and synthetic vitamin diets on mitochondrial function was assessed (**Figure 3**). At the end of the study, the mitochondria from the skeletal muscle were isolated and the DNA content was determined. There was an increase of 175% in the GF diet treated animals over the control and synthetic diet fed mice (**Figure 3(A)**). In **Figure 3(B)**, the changes in mitochondrial enzyme activities were significantly increased in the GF diets compared to control and synthetic diets (**Figure 3(B)**). These included cytochrome c oxidase (COX), b-hydroxyacyl-CoA dehydrogenase (b-HAD) and citrate synthase (CS). COX showed a 215% increase; b-HAD was elevated by 236%; and CS was increased by 156% over control and synthetic diet mice. Next, we examined the expression levels of mitochondrial genes to determine the impact of GF supplementation on mitochondrial activity

(Figure 3(C)). We detected the following changes in mRNAs: PGC-1a—276%; Tfam—221%; ERRa—237%; NRF-1—193%; COXIV—241%; and ATPsyn—183%. These data suggest that there is an increase in mitochondrial activity and function with the treatment of GF diets compared to the control and synthetic diets. There were no significant differences between the GF groups.

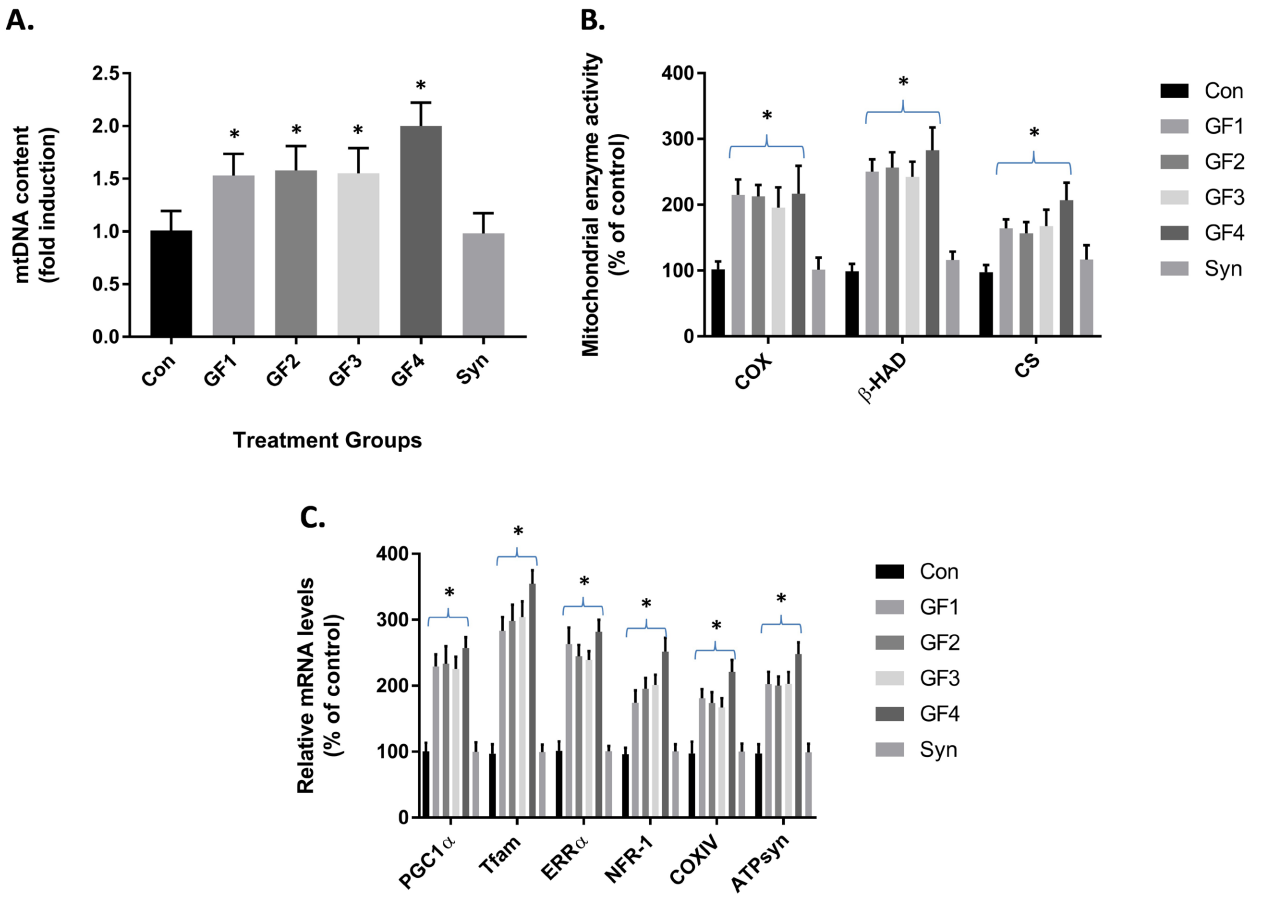

Figure 3. Effect of GF and Syn diets on mitochondrial biogenesis in the muscles of mice. (A) Mitochondrial DNA (mtDNA) quantification in mice fed a control diet, a diet enriched in GF or Syn as determined by the mtDNA/genomic DNA ratio; (B) The activities of mitochondrial enzymes COX, b-HAD and CS were calculated as a percent of control; (C) The relative mRNA levels of PGC-1a, Tfam, ERRa, NRF-1, COXIV and ATPsyn in control, GF or Syn fed mice. The results are expressed as the mean +/− SD (n = 10 per group, *P<0.01 compared to the control group.

3.4. Diet Impact on Signaling in Skeletal Muscle

To determine the impact of the various diets on skeletal muscle function, we determined the effects of the different diets on cell signaling. Studies have shown that AMPK, SIRT1, PGC-1a, and PPARg are essential monitors and controllers of energy metabolism and biogenesis in mitochondria [24]. To this end, our data showed that the GF diets increased the phosphorylation of AMPK and elevated the protein levels of SIRT1, PGC-1a and PPARg when matched to the control and synthetic diets (Figure 4(A) and Figure 4(B)). The following changes were detected: pAMPK—488%; SIRT1—472%; PGC-1a—447%; and PPARg—481%.

S6K1 is a signal of autophagy in cells and the phosphorylated form is elevated in certain conditions. Figure 4(C) and Figure 4(D) are representative of the treatment with GF diets that results in a decrease in the p-S6K1 (70% - 80%) when compared to the control and synthetic diets. In addition, the synthetic diet actually causes an increase in pS6K1. Therefore, we hypothesize that the GF diets appear to stimulate mitochondrial biogenesis and attenuate autophagy [22]. In contrast, synthetic vitamins appear to slow biogenesis, while enhancing autophagy.

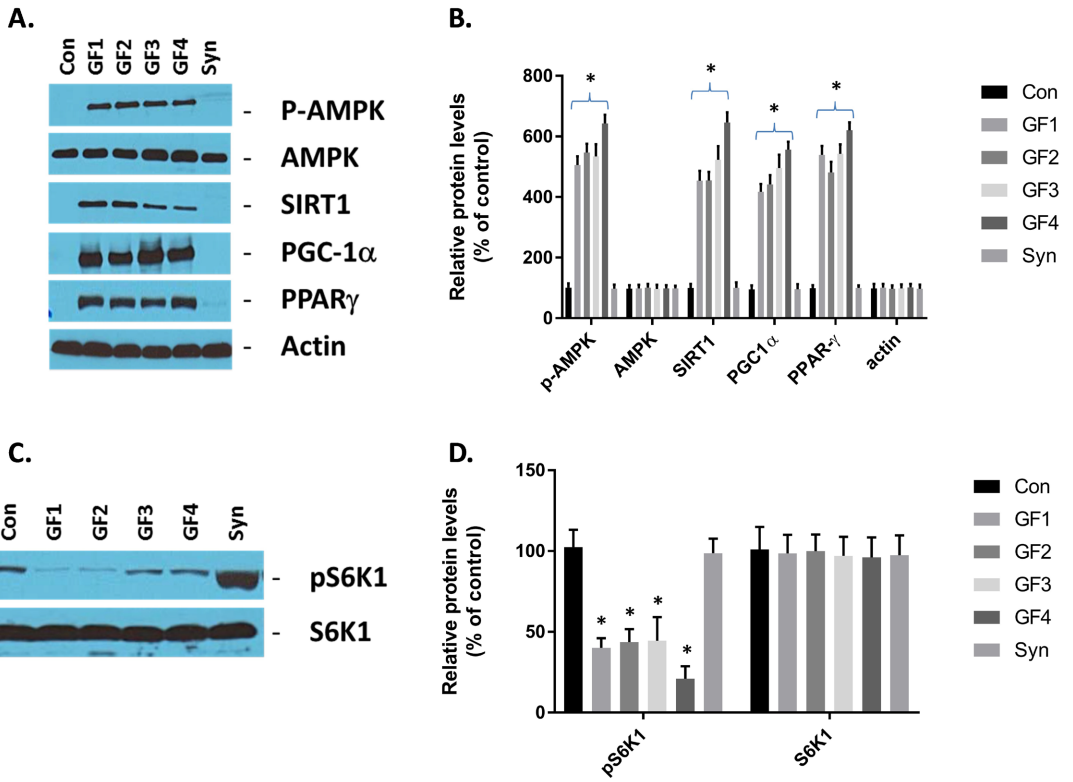

Figure 4. The effect of GF and Syn diets on the exercise signaling pathways and autophagy. (A) The expression of exercise-associated markers such as p-AMPK, AMPK, SIRT1, PGC-1a and PPARg was evaluated by Western blot analysis; (B) The protein expression or phosphorylated levels in (A) were plotted for statistical analysis; (C) Mice fed control, GF or Syn diets were evaluated for p-S6K1 and S6K1 activity; (D) Evaluation of data from (C) The results are expressed as mean +/− SD (n = 10 per group, *P < 0.01 compared to the control group).

4. Discussion

In the current study, we scrutinized the control of mitochondrial function in skeletal muscles by diets rich in vegetables and fruits compared to a synthetic diet and found that exposure to natural diets for 20 weeks increased mitochondria and mitochondrial activity while synthetic vitamins did little to help support mitochondrial function in muscle [24]-[33].

Our bodies need a steady supply of vitamins and minerals to function properly, but they can't produce them on their own. Eating a balanced, nutritious diet is the best way to obtain the essential nutrients, but relying solely on the current food supply can make it challenging to get adequate amounts of vitamins and minerals

required for optimal health [34]. Due to present mainstream farming methods, the soil has been stripped of many vital nutrients, making our food less nutritious [35]. In addition, the shipment of food sources from other countries, which are picked up early and shipped in containers deprived of sunlight and resources, reduces their potential benefit [36]. So, even by consuming a well-rounded, healthy diet, we may still fall short of the recommended daily intake of certain nutrients. Not to mention the constant demands of a hectic, always-on-the-go lifestyle, coupled with anxiety and chronic stress, leaving little time for most people to prepare and consume a wide range of nutrients from natural sources. Today's fast-paced world pushes many to consume processed and fortified foods as they are more convenient and taste better [37]. Unfortunately, processing our foods also strips them of many vital nutrients—contributing to the increasing prevalence of vitamin deficiencies, food allergies, and chronic diseases [38]. Since our food is now nutrient deficient, filling in the gaps with supplements has become increasingly popular in the world of health and nutrition. Consequently, the market for vitamins and dietary supplements has exploded, offering an array of options for consumers. Among these choices, the terms "natural" and "synthetic" vitamins are often seen in our options.

Synthetic vitamins are dietary supplements made artificially in an industrial or laboratory setting to mimic how the body absorbs nutrients from food [39]. They are typically produced through chemical processes that involve the extraction, isolation, and synthesis of specific vitamin compounds [a blend of essential vitamins (A, C, D, E, K, B-complex), minerals (Calcium, Magnesium, Zinc, Iron, Iodine, Selenium), and other nutrients like beta-carotene, often with inactive ingredients for tablet formation (cellulose, gelatin, colorings)]. While synthetic dietary supplements are made to replicate the function and structure of their natural counterparts, they often lack the full range of nutrients, enzymes, and trace minerals found in natural vitamins [40]. It might be best to avoid taking supplements made with synthetic ingredients. As indicated above, synthetic vitamins don't contain trace minerals, enzymes, and co-factors, they can cause deficiencies, they aren't easily absorbed as natural vitamins, they can't be excreted right away, and they can eventually become toxic [41].

Natural supplements are made by concentrating and condensing specific fruits, veggies, and other natural foods into a convenient form that allows the body to get the optimal amount of each nutrient per serving [8]. They typically contain a variety of vitamins, minerals, and other compounds that are found in their food sources, which can provide several advantages over synthetic vitamins: these include synergistic effects and co-nutrients; enhanced absorption and bioavailability; and lower risk of side effects and interactions. Natural supplements are typically produced from plant-based and natural ingredients and do not contain synthetic chemicals or artificial additives, making them less likely to cause harmful side effects and interactions with other prescription medications [42] [43].

Finally, our studies showed a decrease in p-S6K1 which is correlated with

changes in autophagy. Autophagy is a vital, double-edged sword. It plays an essential housekeeping function for health, but its role in disease is complex and depends heavily on the specific cellular context, the stage of the disease, and the overall physiological condition. Modulating autophagy for therapeutic purposes is a promising area of research but requires a nuanced understanding of when to promote it and when to inhibit it [44].

5. Conclusion

In conclusion, the present study has shown that treatment with synthetic vitamins was less effective at therapeutic benefits than natural vitamin supplements. Using synthetic vitamins can pose several dangers to one's health. These include nutrient imbalance, incomplete nutrient profile, poor bioavailability, toxicity risk, lack of synergy and unknown side effects. To mitigate these dangers, it is generally recommended to obtain your vitamins and minerals from a varied diet rich in whole food rather than relying solely on synthetic supplements. Diets enriched with vegetables and fruits that contain natural vitamins and supplements that provide better management of oxidative stress, inflammation and immune dysfunction. Therefore, the utilization of dietary supplements that provide natural sources of vitamins and minerals, and other enhancements are preferable to synthetic versions.

6. Limitations

There are some limitations for the current study. The study was conducted with healthy young mice, and the findings may not be directly generalizable or translatable to other mouse populations, such as aged or diseased mice. However, vitamins are normally taken to improve health and reduce the appearance of disease. In addition, we have previously shown that these diets can improve outcomes from various disorders [15]-[20].

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Author Contributions

J. Y. and M. S. K. were responsible for the study concept and the design. J. Y., H. Z., S. T., C. K. and M. S. K. obtained the data. S. P. and M. S. K. provided data analysis and interpretation. M. S. K. prepared the manuscript. All authors appraised the manuscript for intellectual content. J. Y. and M. S. K. supervised the

work.

Conflicts of Interest

Stephen Perry is an employee of NutriFusion® and has an interest in the company.

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Abbreviations

AMPK	AMP-activated protein kinase
ERRa	estrogen related receptor a
GF	GrandFusion
NRF-1	nuclear regulatory factor 1
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1 α
PPARγ	peroxisome proliferator-activated receptor γ
SIRT1	sirtuin 1
Tfam	mitochondrial transcription factor A