BLS™
BIOENERGY LIFE SCIENCE, INC.

RIBOActiv™

The AMPK Activator

White Paper

These statements have not been evaluated by the Food and Drug Administration.
This product is not intended to diagnose, treat, cure or prevent any disease.

Extend Your Product Line, Broaden Your Market

AMPK is the enzyme that tells your cells to make more energy. And it's creating quite a stir!

AMPK activators are the "what's new" for consumers wanting the latest, greatest advancements in cellular energy. Consumers also crave delivery system variety.

Here's your business-building solution.

Science has revealed that a low, hormetic dose of Bioenergy Ribose — newly branded as RiboActiv — significantly elevates AMPK, leading to more energy, increased antioxidant capacity, better weight management, enhanced blood glucose management, improved blood pressure management and a host of other health benefits.

Even better, "low dose" opens the door to convenient, alternative delivery systems that can expand your market. Your next product may be in the form of oral strips (melts) ... mints ... time-release tablets ... gummies ... food ... beverages ... it's time to innovate!

Clinically validated RiboActiv is a well-established ingredient in a full spectrum of dietary supplements, functional foods, snacks, beverages and much more.

Now demand for this versatile, extensively researched, cellular energy ingredient is expanding into cost-effective dose applications for better health outcomes.

Why Study AMPK and Its Benefits?

Over the past four decades, we have studied D-ribose (RiboActiv) extensively as a dietary ingredient with an initial focus on cardiovascular health. Initially, its reputation was built on the understanding that D-ribose plays a pivotal role in making adenosine triphosphate (ATP), the cells' essential energy currency, thereby supporting heart function. Recent research has unveiled a more detailed picture of how D-ribose truly functions and at lower dosages.

Our preclinical studies revealed that D-ribose's benefits extend beyond energy production. By stimulating nitric oxide production, it contributes to blood vessel dilation and improved blood flow. It also enhances the body's antioxidant defense systems by boosting glutathione levels, and increasing the activity of superoxide dismutase, an enzyme that helps break down potentially harmful molecules.

These many protective mechanisms are thought to be made possible by activating AMPK, an enzyme that has emerged as a key regulator in maintaining a balance of cellular energy. These new findings, combined with what we already know, substantially widen the capacity of D-ribose's potential for supporting health and wellbeing.

AMP-activated protein kinase or AMPK is known as a master metabolic regulator and is a highly sought-after metabolic target for the pharmaceutical, nutraceutical, sport nutrition, and food and beverage industries.

When activated, AMPK increases and replenishes cellular ATP levels. This is associated with weight loss, improved insulin sensitivity, and blood glucose management, as well as reducing inflammation and lowering triglyceride levels in the liver.

This preclinical data aimed to confirm two previous preclinical studies showing a low dose of oral D-ribose was effective at activating AMPK and restoring energy levels in mice, with and without exercise. This study replicated our earlier models, and the results of this study corroborated our previous work.

As a low, hormetic-dose AMPK activator, RiboActiv significantly elevated ATP levels, with and without exercise. RiboActiv's unique mechanism of action through the purine salvage pathway also helps optimize mitochondrial function through the up regulation of citrate synthase.

RiboActiv was also shown to upregulate the PGC-1α, an essential molecule for fat loss and energy metabolism regulation, while improving insulin sensitivity and antioxidant status.

Additionally, AMPK seems to play a role in controlling oxidative stress, which could affect conditions such as type-2 diabetes and its impact on kidney function. A 2018 study published in Antioxidants & Redox Signaling investigated the effect of extracellular superoxide dismutase (EC-SOD) on renal oxidative stress in diabetic nephropathy. The study found that EC-SOD may support kidney health through the activation of AMPK, suggesting that AMPK activation can mitigate oxidative stress.

Understanding AMPK's Significance

When cells are running low on energy, they activate AMPK to restore ATP levels. This process typically happens after intense exercise, or during periods of fasting or calorie restriction.

When activated, AMPK alters the activity of many other genes and proteins. This ultimately results in shutting down anabolic pathways (fatty acid and cholesterol formation) while activating catabolic energy-producing pathways such as glucose uptake and fatty acid oxidation. AMPK is also considered a master switch for glucose and lipid metabolism in various organs, especially in skeletal muscles and the liver.

This means that in addition to boosting energy levels, AMPK activation has several potential benefits:

- **Energize and optimize fat burning.** AMPK upregulates PGC-1α, an important fat loss molecule, and regulates energy metabolism. AMPK and SIRT1 are believed to affect PGC-1α activity directly through phosphorylation. It has also been reported that AMPK, SIRT1, and PGC-1α might act as an orchestrated network to improve metabolic fitness. There is also a substantial overlap in the genes regulated by AMPK and those by PGC-1α, suggesting that PGC-1α might be an essential mediator of AMPK-induced gene expression. AMPK also requires PGC-1α activity to modulate the expression of several key players in mitochondrial and glucose metabolism.
- **Increased mitochondrial volume and enhanced mitochondrial turnover.** Ongoing AMPK activation can lead to up-regulation of citrate synthase, a sign of activity leading to new mitochondrial formation. This helps to clear the body of defective mitochondria and enhance energy production.
- **Improved insulin sensitivity and blood glucose levels.** AMPK activation improves the liver's insulin sensitivity in obese animal models. Also in the liver, it augments fatty acid oxidation and decreases glucose output as well as cholesterol and triglyceride production. In skeletal muscles, AMPK stimulates glucose transport and fatty acid oxidation. These AMPK-induced metabolic effects are associated with lowering blood glucose levels in hyperglycemic individuals.
- **AMPK is a good target for treating non-alcoholic fatty liver disease (NAFLD).** AMPK activation reduces liver triglyceride levels. In a genetic mouse model, it was shown that liver-specific AMPK activation re-programs lipid metabolism, reduces fatty accumulation in the liver, decreases expression of inflammation and fibrosis genes, and leads to significant therapeutic benefits in the context of diet-induced obesity.
- **AMPK activation may benefit those with type-2 diabetes, which is characterized by insulin resistance in key glucose-modulating tissues.** A build up of Reactive Oxygen Species (ROS), or unstable free radicals, can lead to cellular damage. AMPK activation influences several metabolic pathways that indirectly affect cellular ROS levels. For example, by enhancing insulin sensitivity and glucose uptake, AMPK activation can reduce hyperglycemia-induced oxidative stress. Additionally, AMPK's role in lipid metabolism can prevent lipid accumulation and the subsequent production of lipid peroxides, another source of oxidative stress.
- **Enhanced antioxidant status.** D-ribose-activated AMPK leads to increased expression of various antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase, enhancing the cell's ability to neutralize ROS. AMPK activation can also reduce the production of ROS at the source by improving mitochondrial function and efficiency. AMPK reduces electron leakage and subsequent ROS generation in the mitochondria by promoting mitochondrial biogenesis and enhancing fatty acid oxidation.
- **Enhanced endothelial nitric oxide (eNOS).** One exciting and unexpected finding of the preclinical series on AMPK was the enhancement of vasodilation (dilation of blood vessels) in the subjects, independent of exercise. Vasodilation is associated with maintaining healthy blood pressure. The relationship between RiboActiv and eNOS is still unclear but serves to highlight the role of AMPK as a critical regulator of blood vessel health, overlapping therapeutic targets such as cardiovascular intervention.

The Proof Is in the Science

Evaluating D-Ribose and Its Ability to Activate AMPK

The objective of this study was to evaluate the ability of low, low-dose D-ribose on activating AMPK and restoring energy levels in mice.

The following assessments were proven:

- A low, hormetic-dose of RiboActiv activated AMPK phosphorylation and boosted energy as measured by serum ATP levels.
- Increased levels of PGC-1α were found in the liver and skeletal muscles.
- The increased presence of citrate synthase indicated elevated mitochondrial turnover in skeletal muscles and liver tissue.
- Lower blood glucose levels indicating enhanced oxidative metabolism.
- Enhanced antioxidant status which may help with metabolic stress management.

Visualizing Experimental Data

Higher AMPK Activation = Higher ATP Levels

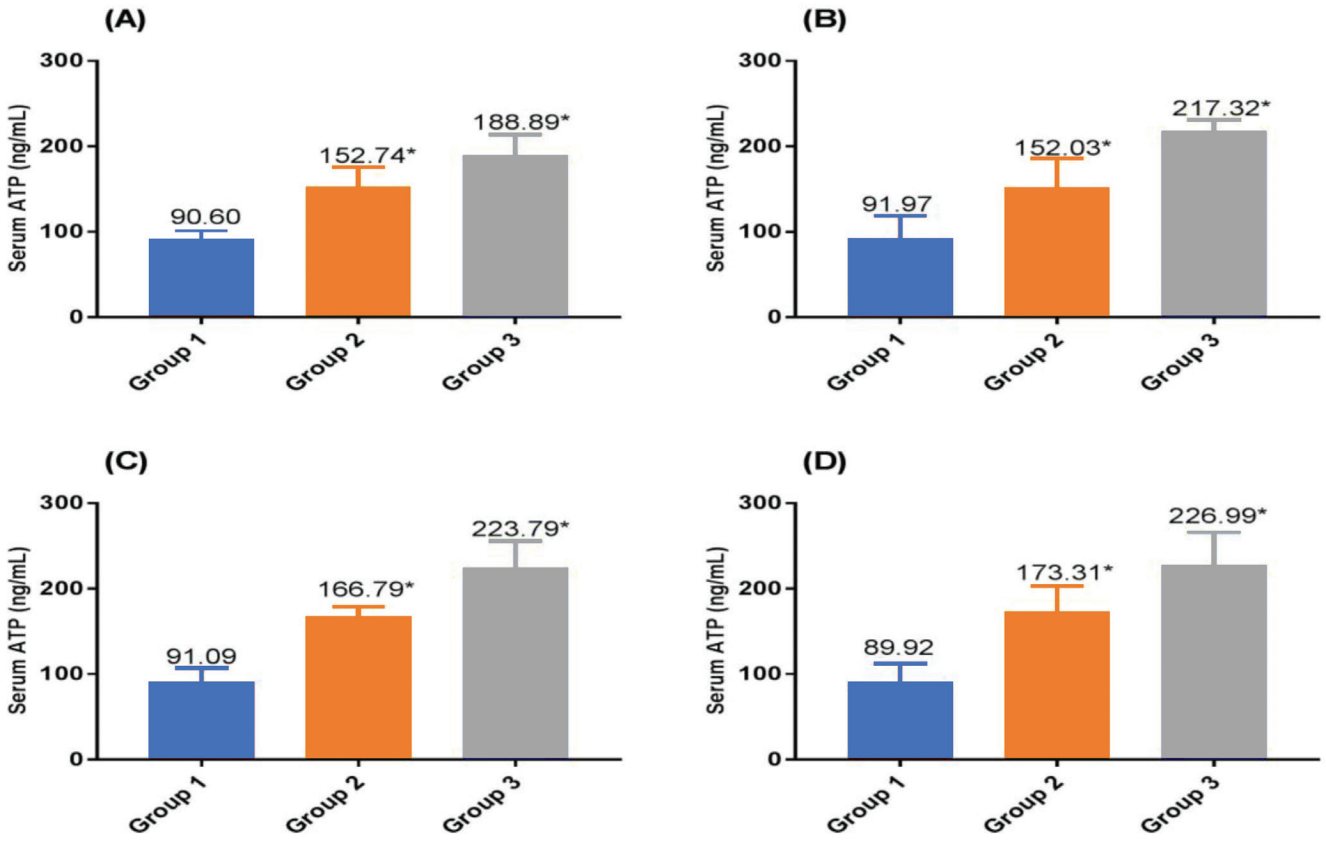

Figure 1A: Summary of serum ATP levels in treatment groups during the treatment period (A) week 1, (B) week 2, (C) week 3 and (D) week 4. (*) Indicates significance concerning Group 1. **Group 1 = Control; Group 2 is Ribose only; Group 3 is Ribose + Exercise.**

More AMPK = Stronger Overall Energy Signal

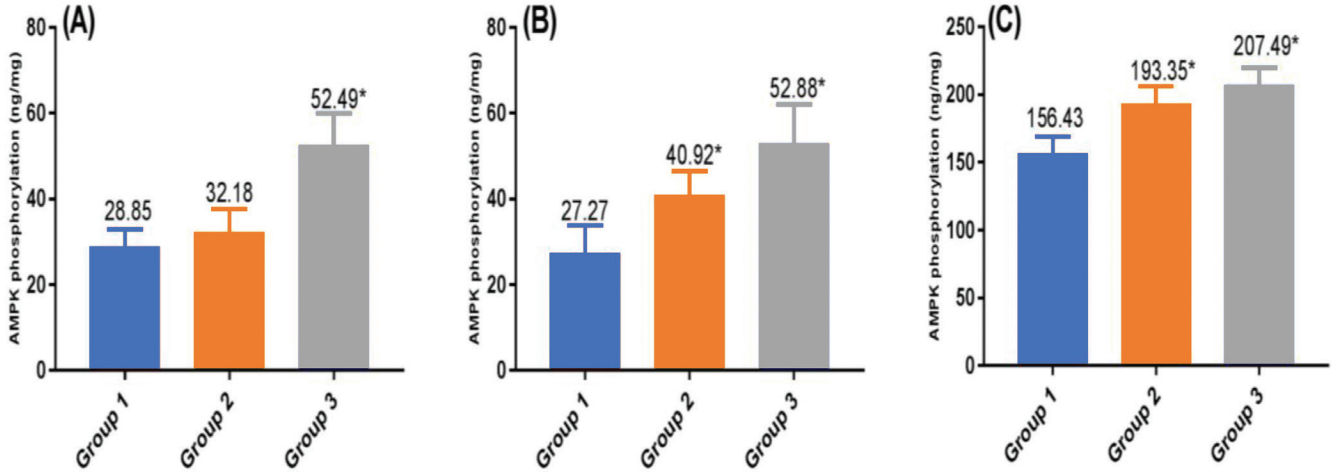

Figure 2A: Summary of AMPK phosphorylation levels in experimental groups during the treatment period (A) Skeletal muscle, (B) Heart and (C) Liver. (*) indicates significance concerning Group 1. **Group 1 = Control; Group 2 is Ribose only; Group 3 is Ribose + Exercise.**

Increase in PGC-1α Protein = Improved Metabolism

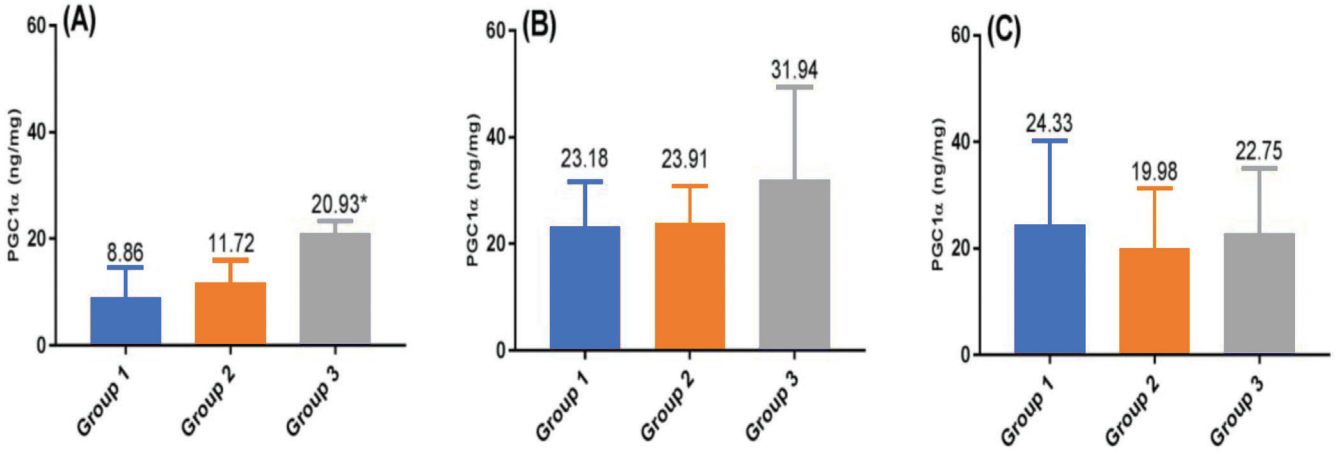

Figure 3A: Summary of PGC-1α protein level in experimental groups during the treatment period (A) Skeletal muscle, (B) Heart and (C) Liver. (*) indicates significance concerning Group 1**. Group 1 = Control; Group 2 is Ribose only; Group 3 is Ribose + Exercise.**

Up-Regulated Citrate Synthase = Elevated Mitochondrial Turnover

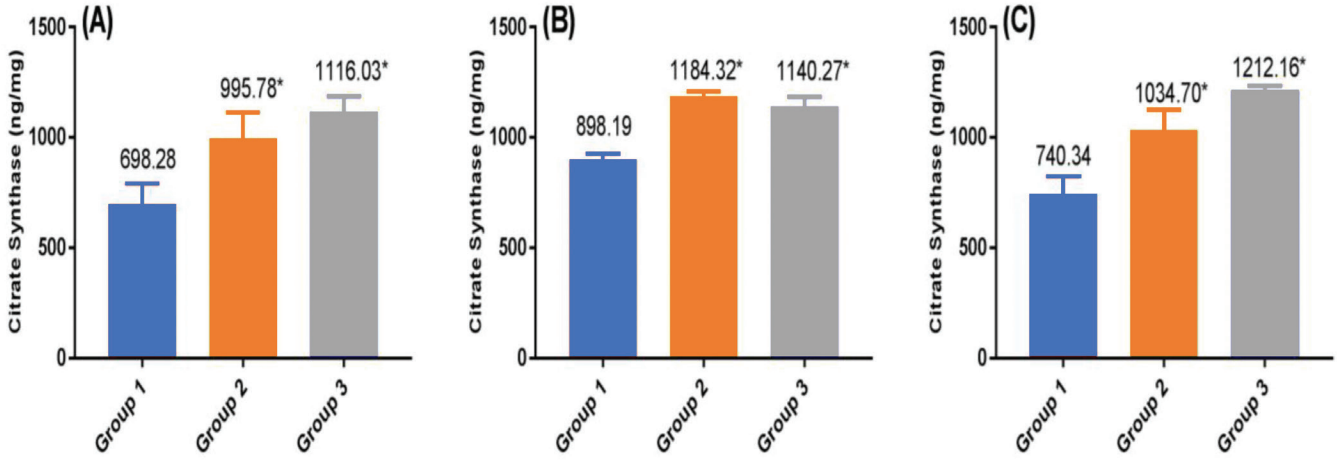

Figure 4A: Summary of citrate synthase levels in experimental groups during the treatment period A) Skeletal muscle, (B) Heart and (C) Liver. (*) indicates significance concerning Group 1. **Group 1 = Control; Group 2 is Ribose only; Group 3 is Ribose + Exercise.**

Visualizing Experimental Data

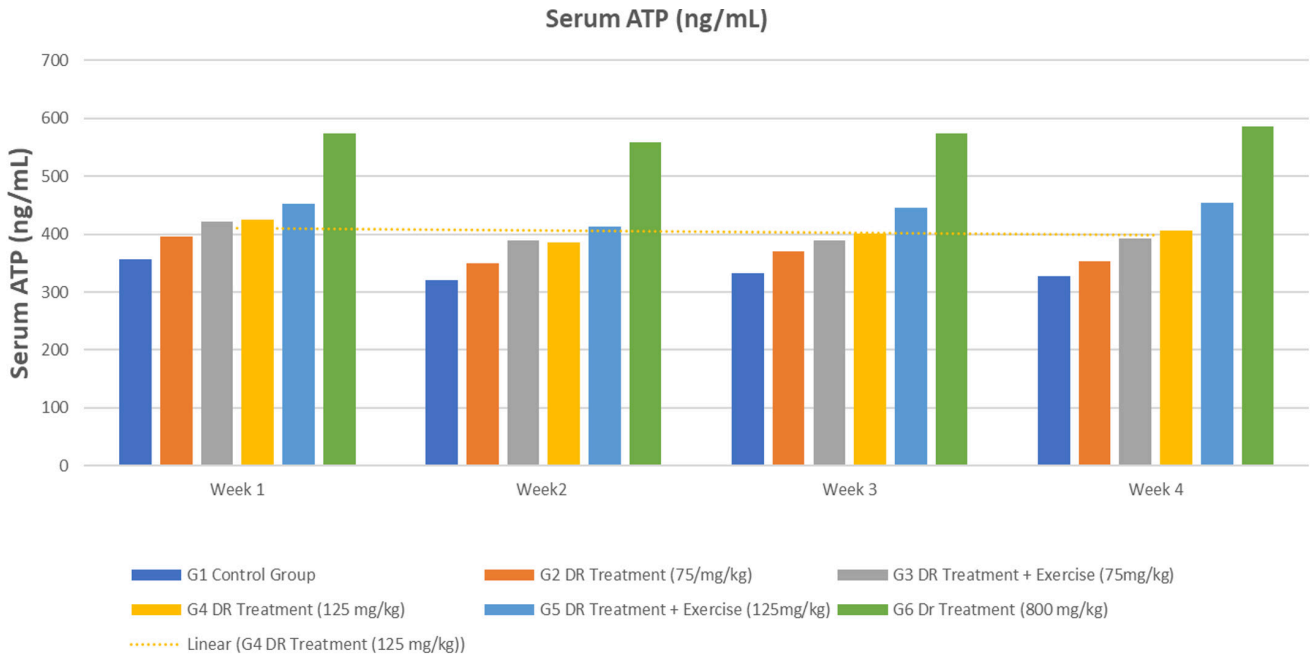

Figure 1B: Summary of weekly serum ATP levels during treatment.

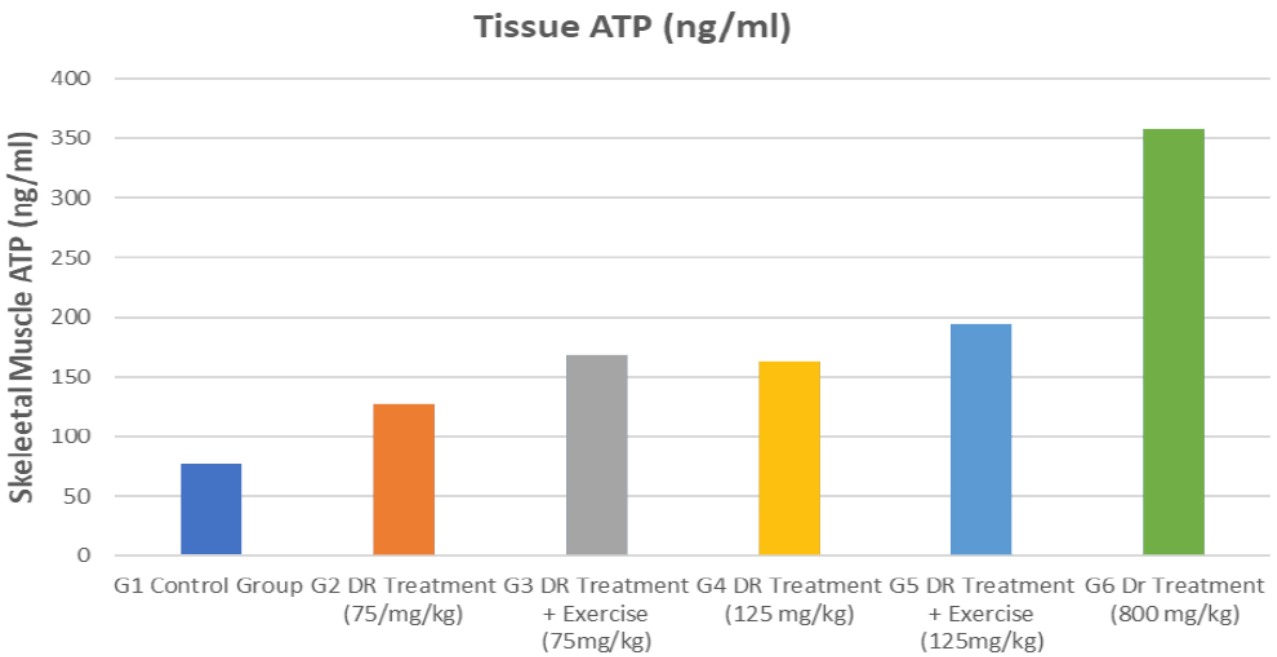

Figure 2B: Summary of ATP levels in skeletal muscle homogenate post-4-week treatment period in different groups.

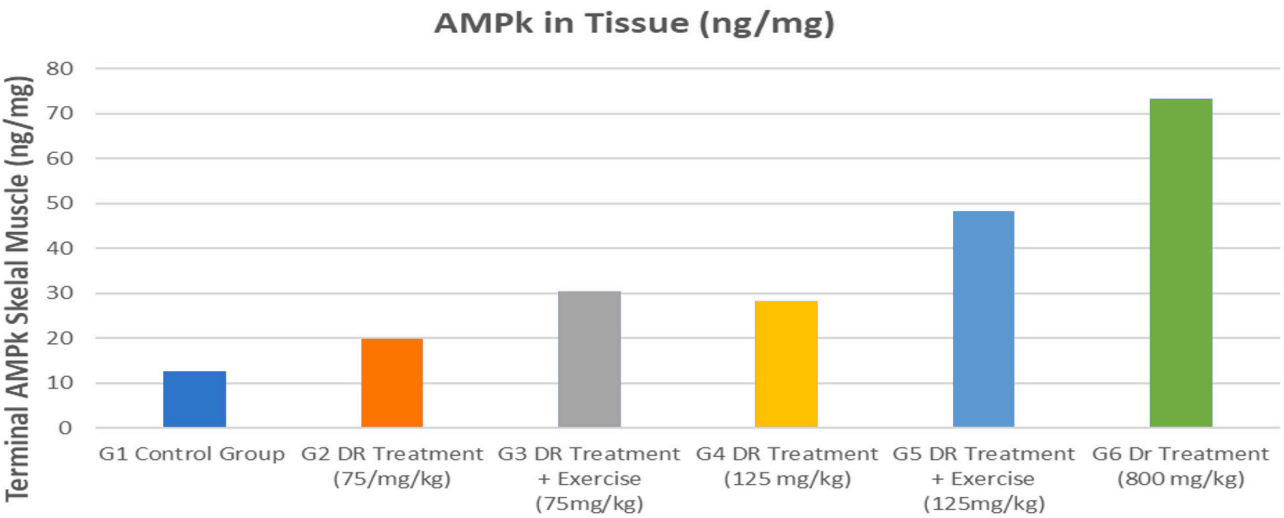

Figure 2C: Summary of p-AMPK levels in different groups' skeletal muscle homogenate post-4-week treatment period.

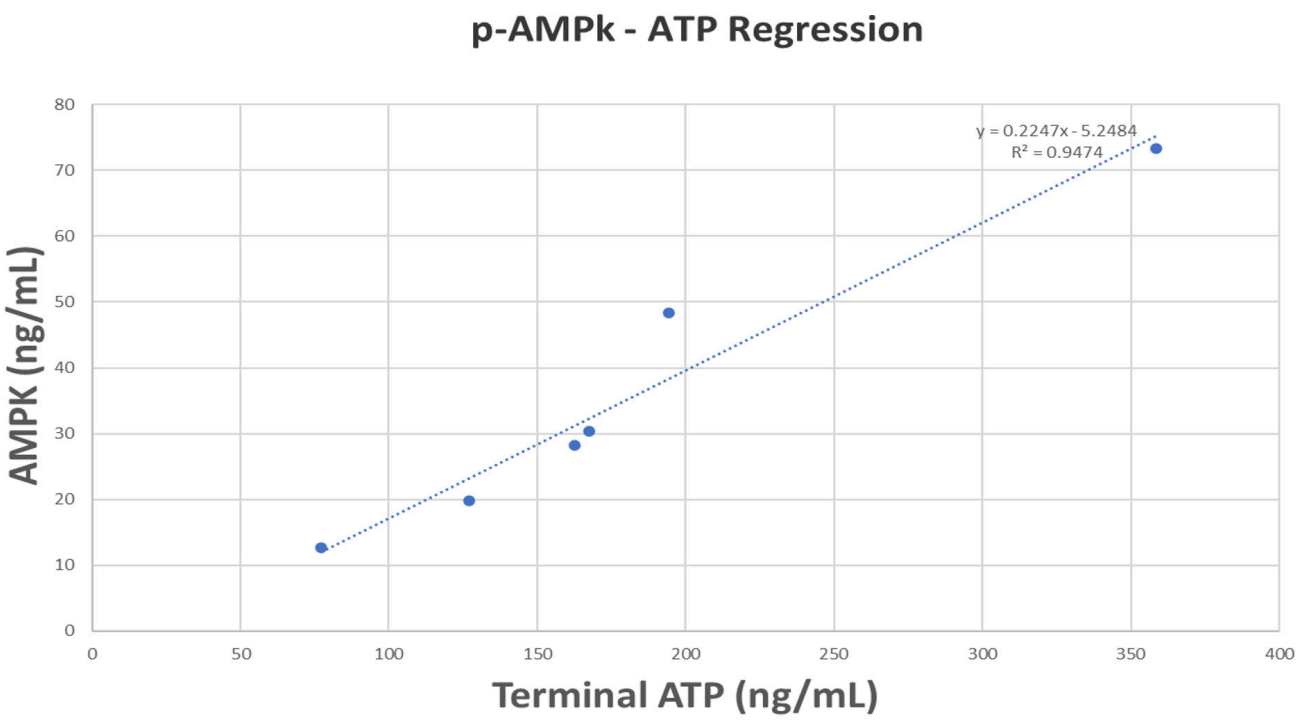

Figure 3A: Summary of the linear fit. p-AMPK signaling is directly causally related to the synthesis and maintenance of ATP. D-ribose administration impacts both parameters independent of exercise.

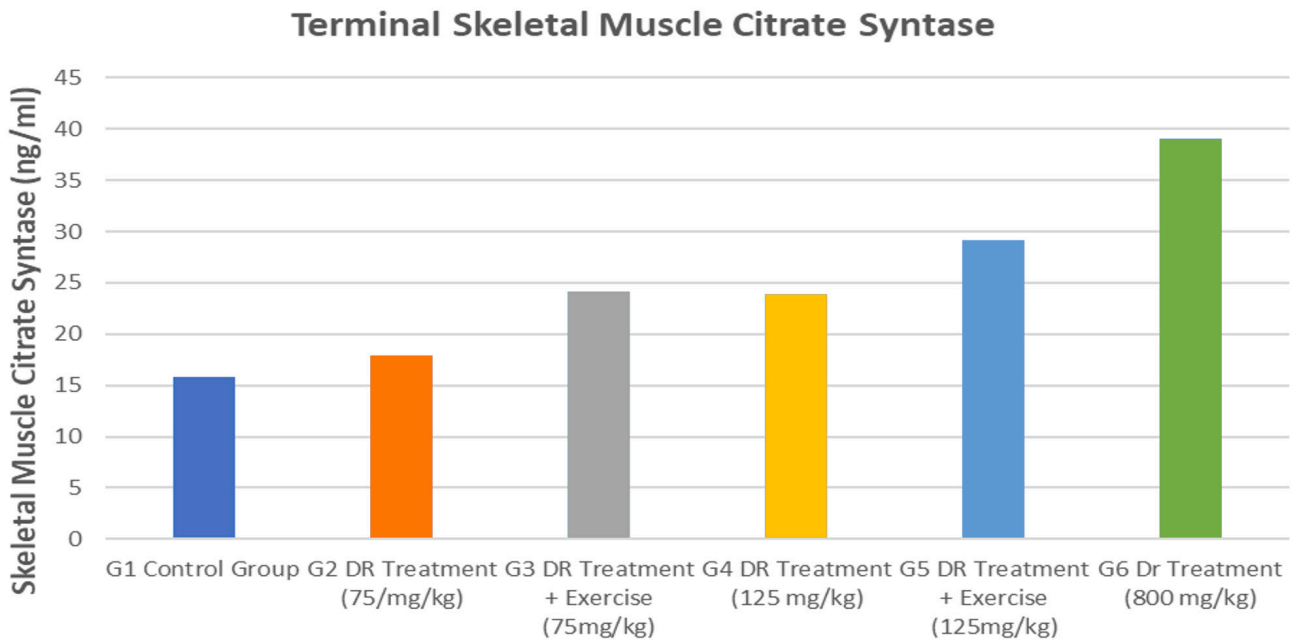

Figure 3B: Summary of citrate synthase in skeletal muscle homogenate post-treatment period.

Anti-Oxidant Capacity and Vasodilation

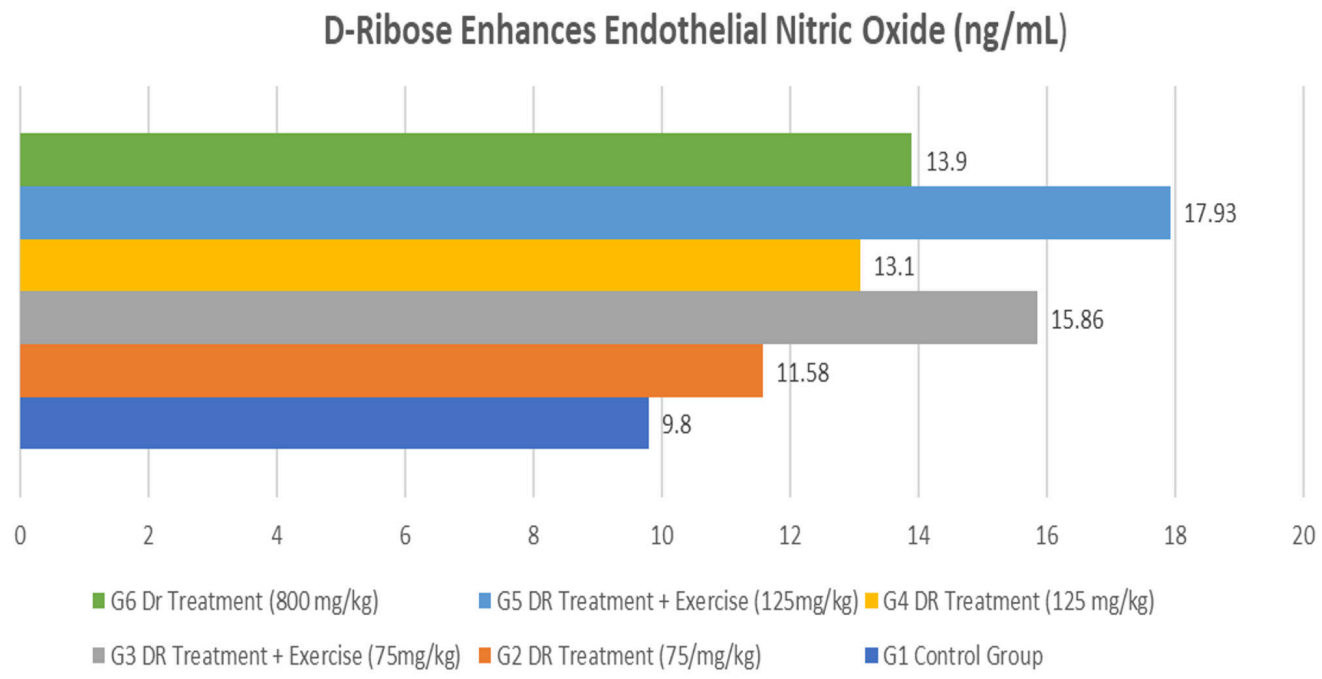

Figure 4B: Summary of endothelial nitric oxide in tissue homogenate post-treatment in exercising and non-exercising mammals.

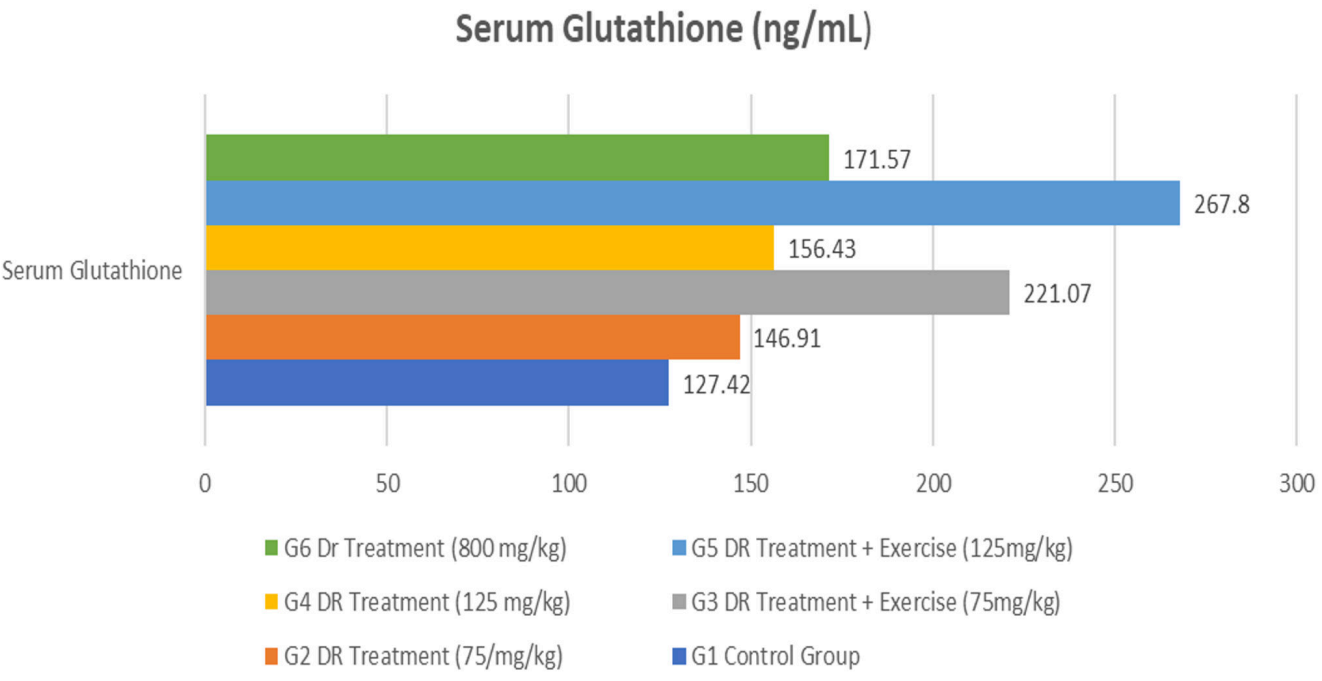

Figure 5B: Summary of serum glutathione post-treatment period in exercising and non-exercising mammals.

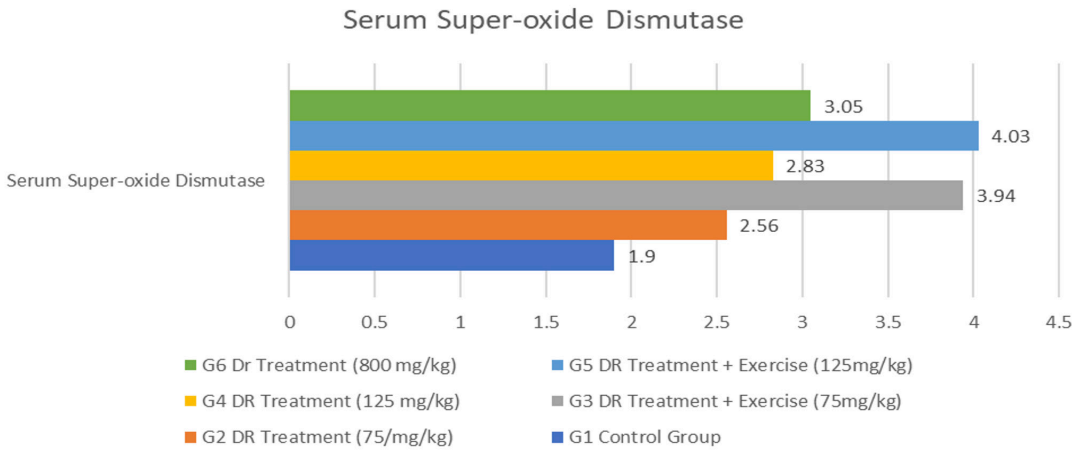

Figure 6B: Summary of serum superoxide dismutase post-treatment.

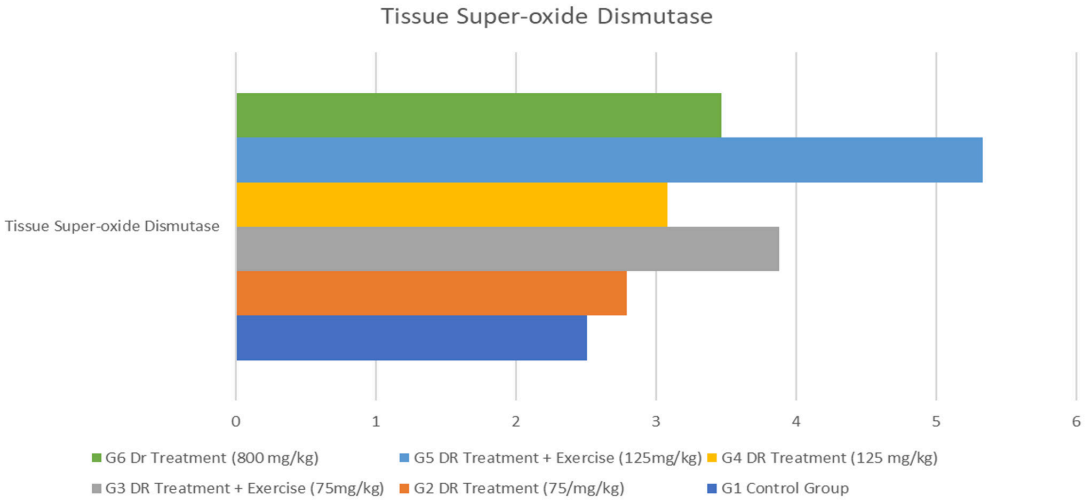

Figure 7B: Summary of tissue super-oxide dismutase post-treatment.

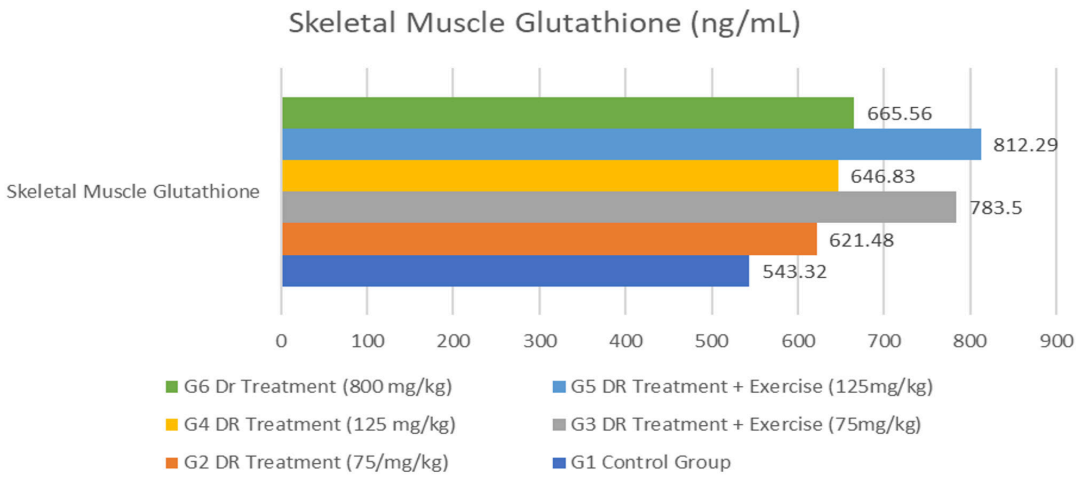

Figure 8B: Summary of tissue glutathione post-treatment.

Blood Glucose and Insulin Management

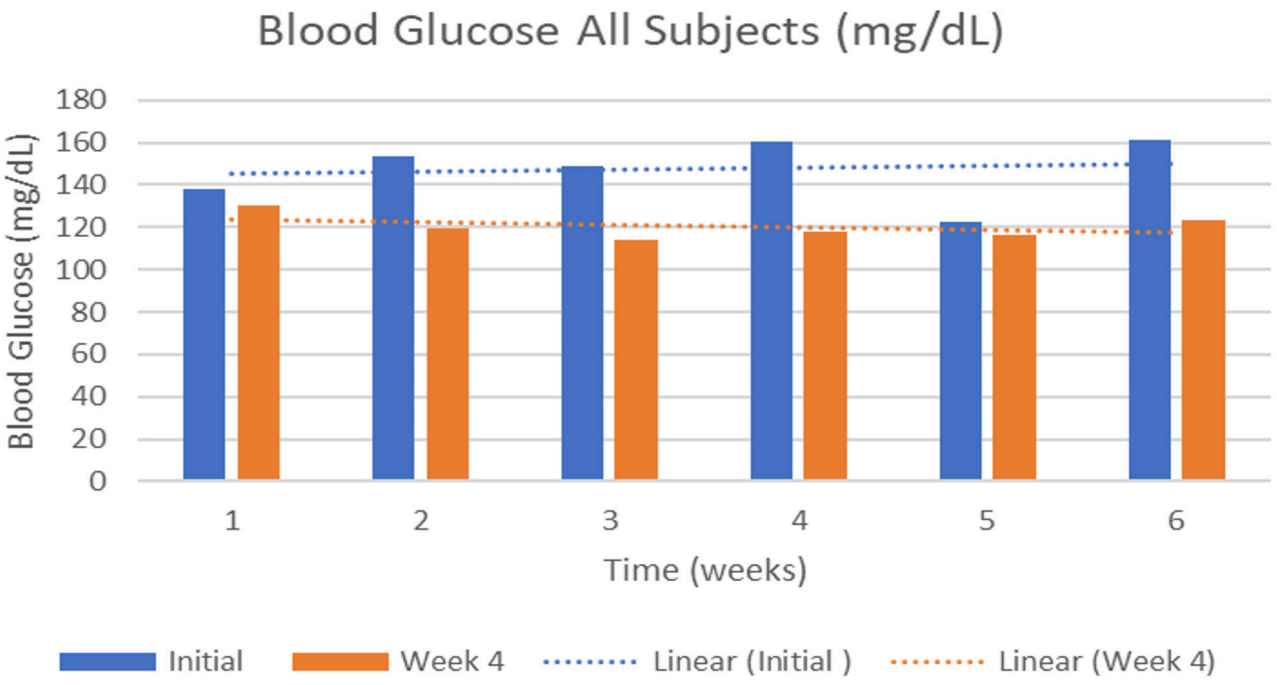

Figure 9B: Summary of all subjects blood glucose levels over the treatment period.

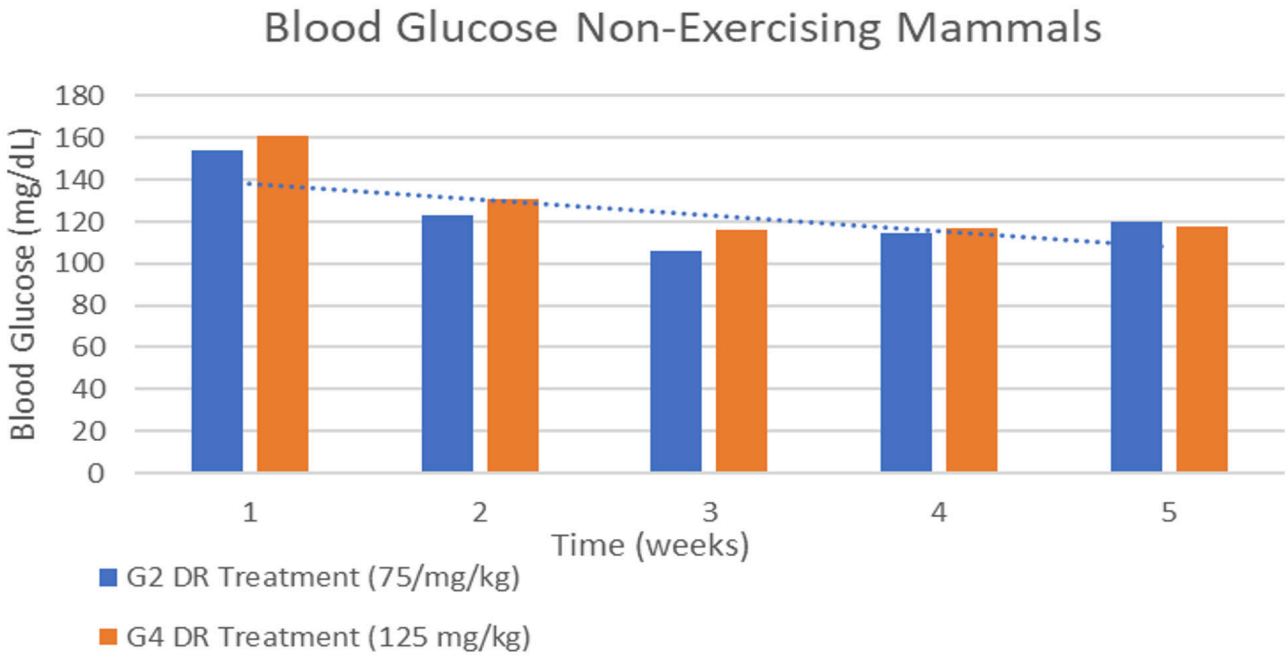

Figure 10B: Summary of blood glucose in non-exercising mammals over the treatment period.

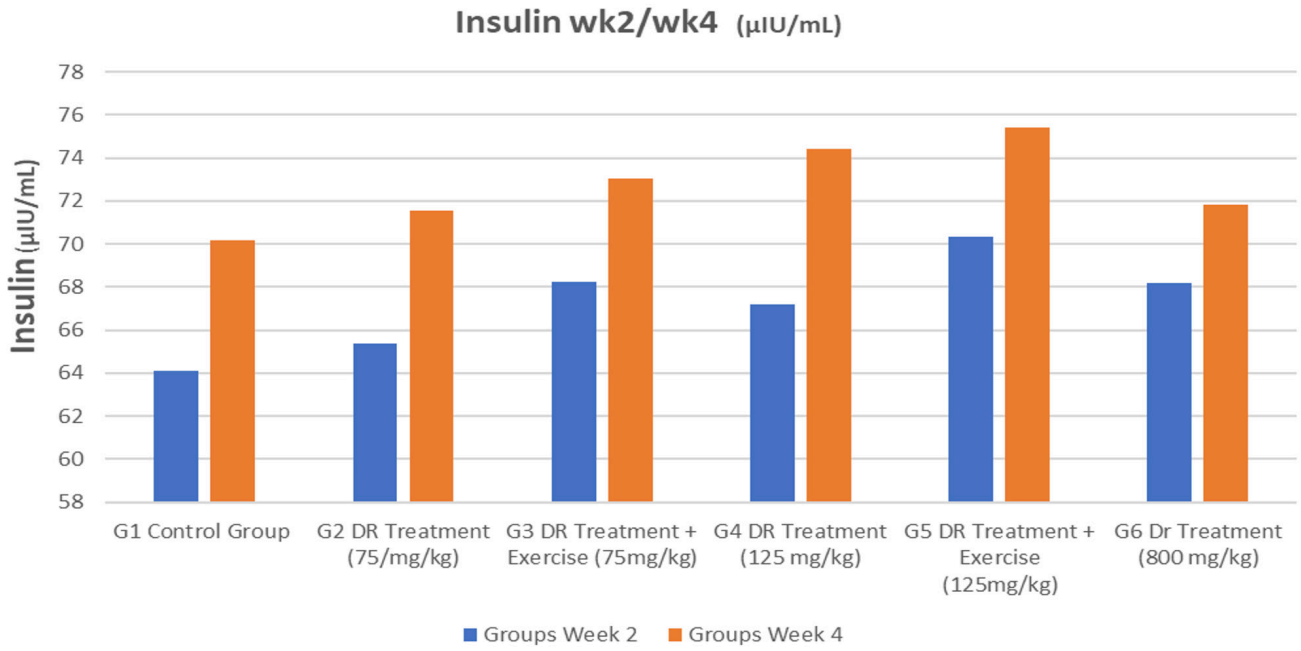

Figure 9B: Summary of insulin signaling in all subjects at weeks two and four over the treatment period.

The Power of RiboActiv

RiboActiv Increases AMPK With or Without Exercise

For over four decades, D-ribose (RiboActiv) has been a focal point of scientific inquiry, with research evolving from its role as a dietary ingredient for cardiovascular health to its increasing potential in sports and performance enhancement. Historically, D-ribose's claim to fame was its critical function in the production of adenosine triphosphate (ATP), the cellular energy powerhouse vital for sustaining the high-energy demands of both the heart and muscles during intense physical activity.

Recent studies have uncovered that D-ribose also contributes to blood vessel dilation (vasodilation), by helping to make nitric oxide which improves blood flow. It has also been shown to enhance the body's antioxidant capabilities by increasing glutathione and superoxide dismutase levels. These effects are made possible by activating AMPK, an enzyme that is a master switch in cellular energy regulation,

The relationship between AMPK activation and antioxidant status is characterized by a direct increase in cellular antioxidant defenses, reduction of ROS free radical production, and modulation of metabolic and signaling pathways that collectively enhance the cellular antioxidant capacity, which is a measure of cells' ability to withstand oxidative damage.

This makes AMPK a critical target for interventions aimed at maintaining the health of organs and systems — including kidneys and blood vessels — that may be impacted by metabolic syndrome, type-2 diabetes, cardiovascular diseases, and neurodegenerative disorders.

Pre-clinical data observed that the oral administration of a low, hormetic-dose of RiboActiv rapidly increased serum ATP in sedentary animals independent of exercise.

Researchers also observed:

- Combining exercise with RiboActiv treatment further increased serum ATP levels.
- Significant elevation of AMPK in liver, heart and skeletal muscle tissue independent of exercise, indicating the power of RiboActiv to increase AMPK.
- Along with elevated ATP, levels of phosphorylated AMPK, PGC1α and citrate synthase also increased significantly in major organs such as the liver, heart and skeletal muscles.
- Treatment with RiboActiv did not lead to a significant alteration in feed intake and body weight gain during the study.

These studies concluded that an oral low, hormetic-dose of RiboActiv activates AMPK (with our without exercise), efficiently boosts serum ATP levels, and helps to maintain energy levels during strenuous exercise. It can stimulate the activation of genes known to be up regulated during exercise, which can add to the beneficial effects of regular exercise on health and wellness.

**A patent application was submitted following three pre-clinical trials designed to reproduce and expand upon the initial study's findings. Methodology and results will be made available upon confirmation of patent filing, and submission of journal articles for publication.*

Declaration

The study entitled "AMPK Activation after Oral Treatment with Ribose in Exercising Mice" was performed in accordance with Standard Operating Procedures and signed Study Plan. No circumstances in the study have been left unreported which might have influenced the quality or integrity of the study.

The study was approved by the Institutional Animal Ethics Committee and animals used in the experiment were handled as per AAALAC Guidelines.

This is also to certify that the results presented in this report are complete, true and accurate reflection of the raw data obtained during the conduct of the study.

This research was performed by:

Vedic Lifesciences Pvt. Ltd. 118, Morya House, Andheri West, Mumbai, Maharashtra India

Conclusion

With this preclinical data, new scientific evidence now consistently demonstrates that supporting the body's natural energy pathways with RiboActiv produces wellness benefits above and beyond just fueling cellular energy, and improving sport performance and reducing muscle recovery.

We have discovered only RiboActiv is confirmed to activate AMPK with a unique mechanism of action through the purine salvage pathway.

The far-reaching implications for AMPK activation include improved weight loss, increased mitochondrial volume and enhanced mitochondrial turnover, as well as improved insulin sensitivity and blood glucose levels.

Formulating with a low, hormetic-dose of RiboActiv also gives you the assurance that you are using:

- The only Ribose that's GRAS (Generally Recognized as Safe) Certified from the FDA and Novel Food Approved from EFSA.
- The only Ribose that's Non-GMO Project Verified and BRC Certified.
- The cleanest, purest Ribose on the market.
- The only Ribose on the market that is Scientifically Proven, Patented with available health claims and Regulatory Support.

BLS is The Ribose Company™, with the scientific research, product development experience and value-added services to support you.

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White Paper

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