SENACTIV®

ENDURANCE, ENERGY, RECOVERY, FITNESS, LONGEVITY

Validated in 2 *in-vivo* and 4 human clinical trials, evaluating 6 different interventions

Published in PLOS One
Journal of Ginseng Research
Journal of the International Society of Sports Nutrition
Evidence-based Complimentary and Alternative Medicine
Journal of Functional Foods
Journal of Science in Sport and Exercise
Aging

US Patent No. 10,806,764

NPN 80086984

GRAS/NDI Self-affirmed

Pennies per serving

GRAS Affirmed
GENERALLY RECOGNIZED AS SAFE

INFORMED CHOICE
INGREDIENT

nulivscience.com

DISCOVER SENACTIV®

Senactiv® is NuLiv Science's proprietary sports nutraceutical composed of two highly purified and fractionated extracts from *Panax notoginseng* and *Rosa roxburghii* produced by a NuLiv Science pharmaceutical extraction and processing technology.

Senactiv® is the result of over ten years of research that has shown in 2 *in-vivo* as well as 4 human clinical studies, evaluating 6 different interventions published in PLOS One, Journal of Ginseng Research, Journal of the International Society of Sports Nutrition, Evidence-based Complimentary and Alternative Medicine, Journal of Functional Foods, Journal of Science in Sport and Exercise, and Aging to:

- increase endurance time (time to exhaustion) by 20% in a high-intensity (80% $V0_2$max) cycling exercise time to exhaustion in human clinical trial published in PLOS One.
- increase energy production by producing 47% more pace-making enzyme citrate synthase in the citric acid cycle (ATP production) in muscle cells in a vigorous (70% $V0_2$max) 60 minute cycling exercise in another human clinical trial published in PLOS One.
- speed up muscle recovery by reducing inflammation in muscles (24% in TBARS, 44% in MDA, 35% in IL-6, and 69% in CK) and increasing muscle glycogen buildup by 273% in a vigorous (70% $V0_2$max) 60 minute cycling exercise or a weight lifting exercise in a third human clinical trial published in PLOS One.
- eliminate senescent muscle cells through macrophage phagocytosis in a fourth human clinical trial published in Journal of Ginseng Reasearch. Specifically, to decrease SA-β-gal and collagenase, reverse apoptotic DNA fragmentation and leukocyte infiltration, and increase iNOS and IL-6 mRNA expression in quadriceps (*vastus lateralis*) after a 60 minute cycling exercise at 70% $V0_2$max.
- increase Myf5 mRNA and restore satellite cell numbers and total glutathione and centrally nucleated myofibers 3h post-exercise in a human clinical trial published in Journal of Functional Foods. Satellite cells give rise to differentiated muscle cells.
- rapidly regenerate new muscle cells by restoring satellite cell numbers after a 60 minute cycling exercise at 70% $V0_2$max as evidenced by increased Pax7 and Myf5 proteins and centrally nucleated muscle cells in a human clinical trial published in the Jounral of Functional Foods.
- Clear senescent cells in muscle and stimulate tissue repair after a 60 minute $V0_2$max cycling exercise by the clearance of $P16^{ink4a}$ and decreased IL-10 mRNA in a human clinical trial published in Aging.
- decrease senescent cell and triggers cell renewal and growth to increase physical fitness and life expectancy.

HOW SENACTIV® WORKS

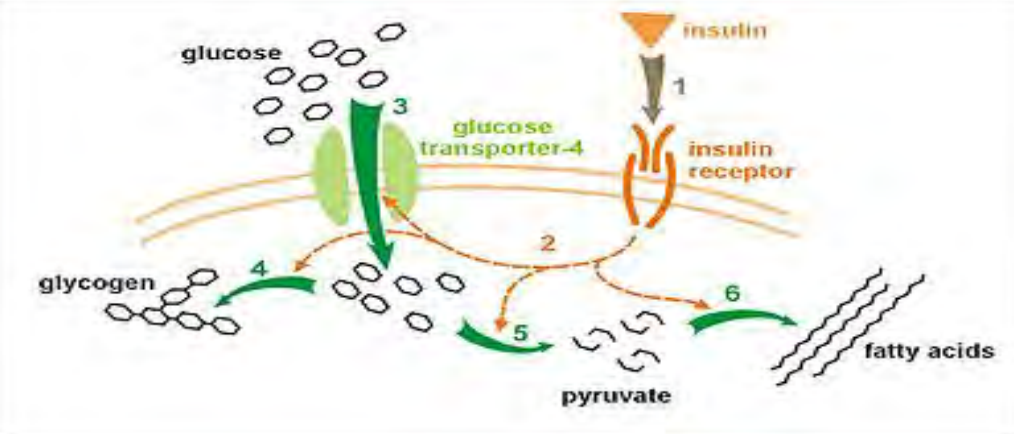
Muscle Fatigue Recovery

TBARS ↓

MDA ↓

IL-6 ↓

CK ↓



Endurance & Energy

Glycogen ↑

CS ↑

GSH ↑

Insulin Sensitivity ↑

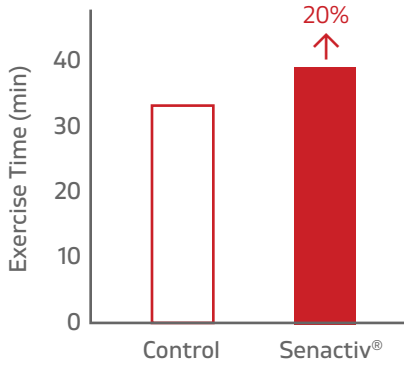
Two *in-vivo* and four human clinical studies evaluating six different interventions on Senactiv® suggest that its effects on improving endurance/stamina, energy and recovery time in high-intensity exercises may be due to its ability to preserve insulin receptors and glucose transporters on muscle membrane during intensive exercises to ensure a continuous supply of blood glucose into muscle. Glucose is the fuel for muscle during intensive exercise. Depletion of glucose has detrimental effects for muscles to contract and work properly.

There are senescent cells in all human tissues at certain proportions, particularly for those short-lived endothelial cells (lifespan < 2 weeks) in blood vessels of tissues. Senactiv® substantially reduced senescent cell population (mostly endothelial progenitor cells) of exercising skeletal muscle (JGR). Exercise challenge acutely decreases satellite cell numbers due to increased demand on nucleus for muscle regeneration during challenges. Senactiv® completely attenuated acute satellite cell depletion (JFF). These findings suggest that Senactiv® effectively facilitates senescent cell clearance in contracting muscles and helps maintain muscle stem cell numbers during exercise to enhance high intensity endurance performance.

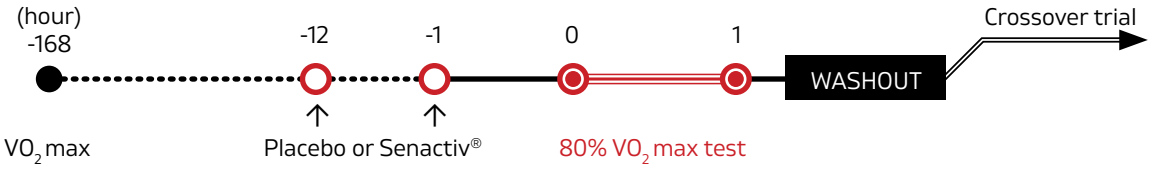
SENACTIV® IMPROVES 60 MIN HIGH-INTENSITY CYCLING (80% VO_2MAX) TIME TO EXHAUSTION BY 20% (1, 2)

Senactiv® was shown in a randomized double-blind placebo controlled crossover human clinical trial (1) to increase the time to exhaustion in high-intensity cycling (80% VO_2max) by 20%.

Based on the findings from the other human clinical trials on Senactiv®, we propose that the improved endurance may be due to Senactiv®'s ability to meet the increased energy demand in glycogen and ATP in muscle during intense exercise by increasing ATP (in citrate synthase (1)) production, by preserving the insulin pathway to mitigate the interruption of glucose supply to muscle cells (1), and by scavenging the senescent muscle cells produced during the intense exercise (2).



Study Design on Senactiv®'s Ergogenic Action

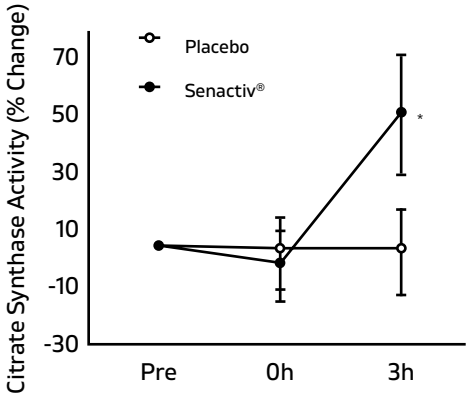


1. Hou, C.-W., Lee, S.-D., Kao, C.-L., Cheng, I.-S., Lin, Y.-N., Chuang, S.-J., ... Kuo, C.-H. (2015). Improved Inflammatory Balance of Human Skeletal Muscle during Exercise after Supplementations of the Ginseng-Based Steroid Rg1. *Plos One*, 10(1). doi: 10.1371/journal.pone.0116387

2. Wu, J., Saovieng, S., Cheng, I.-S., Liu, T., Hong, S., Lin, C.-Y., ... Kuo, C.-H. (2018). Ginsenoside Rg1 supplementation clears senescence-associated β-galactosidase in exercising human skeletal muscle. *Journal of Ginseng Research*. doi: 10.1016/j.jgr.2018.06.002

SENACTIV® INCREASES ENERGY LEVEL IN 60 MIN CYCLING (70% VO_2MAX) BY 47% (1)

Senactiv® was shown in a randomized double-blind placebo-controlled crossover human clinical trial (1) to increase the citrate synthase in muscle by 47% after a 60 min cycling exercise at 70% VO_2max. Citrate stands as a pace-making enzyme in the first step of the citric acid cycle that produces ATP, the energy currency of cells.

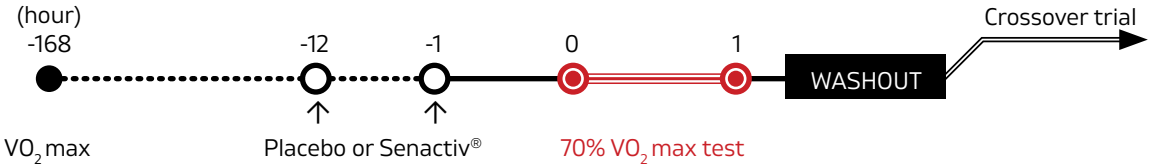


Relative citrate synthase activity in indicated time after exercise

CS Activity (%)	Placebo Group	Senactiv® Group
0 hrs After Exercise	100.0±12.38	94.60±12.43
3 hrs After Exercise	100.0±14.76	147.23±19.77*

*Significant difference against placebo group., p<0.05

Study Design on Senactiv®'s Anti-inflammatory Effect on Muscles After Exercise

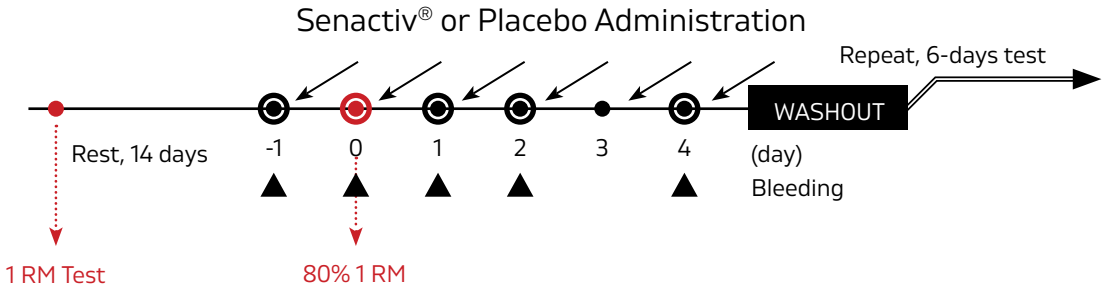


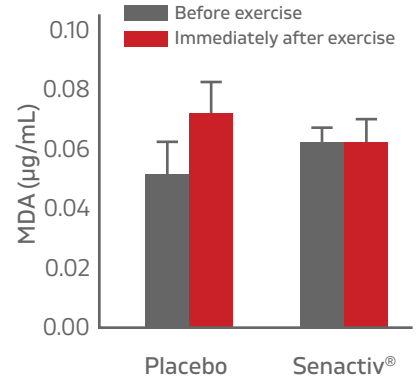
1. Hou, C.-W., Lee, S.-D., Kao, C.-L., Cheng, I.-S., Lin, Y.-N., Chuang, S.-J., ... Kuo, C.-H. (2015). Improved Inflammatory Balance of Human Skeletal Muscle during Exercise after Supplementations of the Ginseng-Based Steroid Rg1. *Plos One*, 10(1). doi: 10.1371/journal.pone.0116387

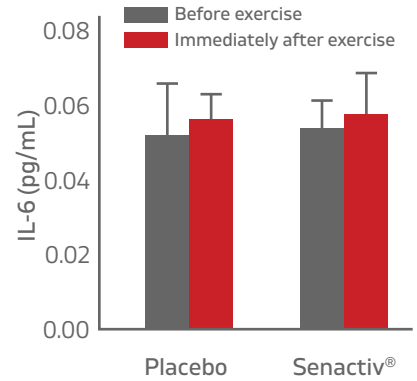
SENACTIV® SPEEDS UP MUSCLE RECOVERY BY MITIGATING INFLAMMATORY RESPONSE AFTER STRENUOUS EXERCISE (1, 2)

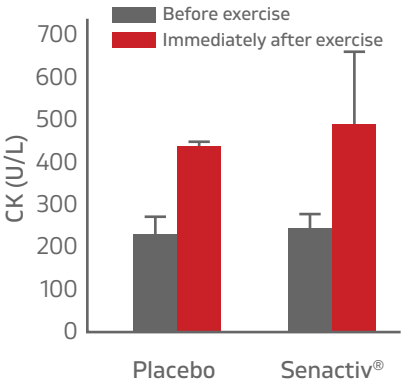
- Reduces lipid peroxidation marker TBARS by 24% after a 60 min cycling exercise at 80% VO_2max (1).
- Reduces free radical damage to muscle after exercise (MDA synthesis) by 44% on day 4 after a weight lifting exercise.
- Reduces inflammation by decreasing IL-6 synthesis by 35% on day 4 after a weight lifting exercise.
- Decreases Creatine Kinase (CK) on day 4 by 69% after a weight lifting exercise. Plasma CK reflects leakage of protein from skeletal muscle to circulation, which normally occurs after vigorous exercise.

Prolonged exercise increases cellular membrane peroxidation (mirrored by increased TBARS or MDA), which has been suggested to disrupt normal cellular insulin and glucose signaling pathways on sarcolemma and glycogen synthesis in muscles. Senactiv® minimizes such unwanted oxidative damage produced during physical exertion, and ultimately enhances the robustness of our body to sustain prolonged intensive exercise.







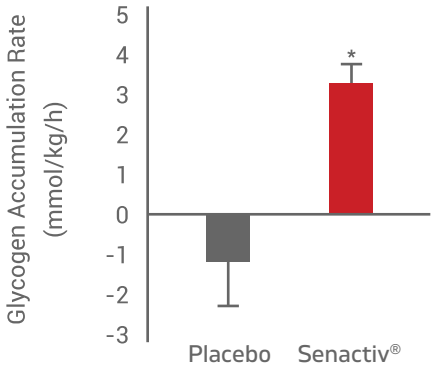


1. Hou, C.-W., Lee, S.-D., Kao, C.-L., Cheng, I.-S., Lin, Y.-N., Chuang, S.-J., ... Kuo, C.-H. (2015). Improved Inflammatory Balance of Human Skeletal Muscle during Exercise after Supplementations of the Ginseng-Based Steroid Rg1. *Plos One*, 10(1). doi: 10.1371/journal.pone.0116387

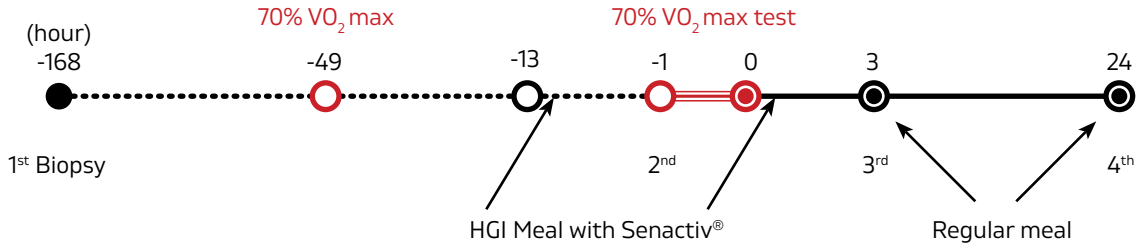
2. Wu, J., Saovieng, S., Cheng, I.-S., Liu, T., Hong, S., Lin, C.-Y., ... Kuo, C.-H. (2018). Ginsenoside Rg1 supplementation clears senescence-associated β-galactosidase in exercising human skeletal muscle. *Journal of Ginseng Research*. doi: 10.1016/j.jgr.2018.06.002

SENACTIV® SPEEDS UP MUSCLE RECOVERY BY INCREASING MUSCLE GLYCOGEN SYNTHESIS (1)

Subjects performed an acute bout of 60 min of cycling at 70% VO_2max. Vastus lateralis samples were collected at 0 h and 3 h post-exercise for determining the rate of glycogen storage. The rate of 3 h glycogen accumulation was elevated by 2.73 fold with Senactiv® ingested the night before and immediately after a glycogen-depleting exercise.



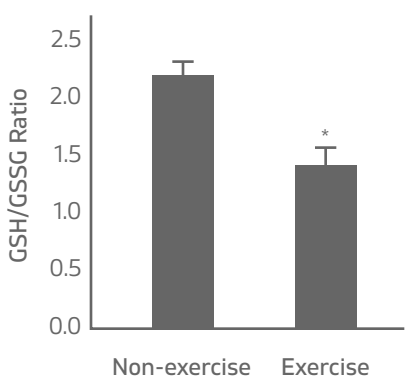
Study Design on Senactiv®'s Glycogen Recovery Rate in Muscles After Exercise

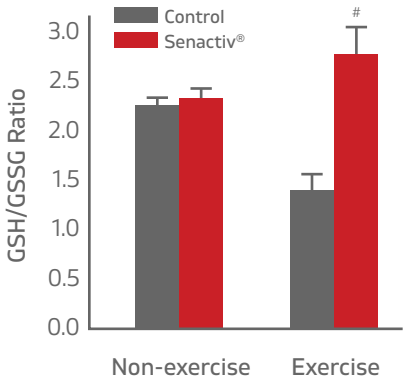


Muscle glycogen is the main fuel for strenuous sports activity. Senactiv® increased the rate of glycogen re-synthesis after 1 h cycling at 70% VO_2max by 373%. This 2.73 fold increase improves fatigue recovery from acute physical challenge for prolonged aerobic and anaerobic activities. It is suggested that the mechanism may be due to its ability to up-regulate the Adiponectin secretion to affect AMPK-GLUT4 mediated glucose absorption in muscle cells.

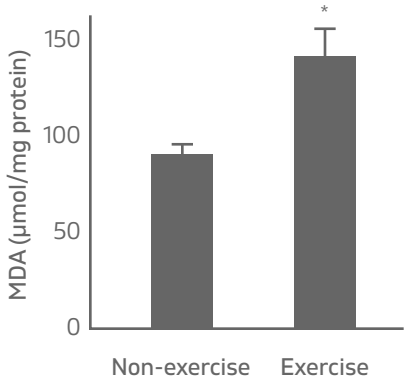
1. Hou, C.-W., Lee, S.-D., Kao, C.-L., Cheng, I.-S., Lin, Y.-N., Chuang, S.-J., ... Kuo, C.-H. (2015). Improved Inflammatory Balance of Human Skeletal Muscle during Exercise after Supplementations of the Ginseng-Based Steroid Rg1. *Plos One*, 10(1). doi: 10.1371/journal.pone.0116387

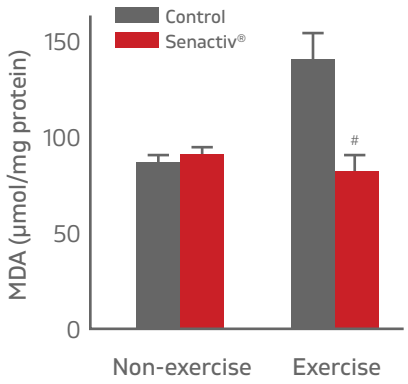
SENACTIV® REDUCES INFLAMMATION IN EXHAUSTED EXERCISE-INDUCED SARCOLEMMA LIPID PEROXIDATION IN RATS (3)





Senactiv® on muscle GSH/GSSG ratio
* significant difference against non-exercise group.
# significant difference against control group.





Senactiv® on muscle MDA levels
* significant difference against non-exercise group.
# significant difference against control group.

Exercise-induced oxidative stress causes temporary membrane lipid peroxidation (MDA level), which was protected by Senactiv® supplementation by preserving the GSH/GSSG ratio. Sarcolemma integrity is essential for transmembrane glucose transport and normal insulin signaling. Normal insulin signaling is required for triggering muscle glycogen synthesis.

3. Yu, S.-H., Huang, H.-Y., Korivi, M., Hsu, M.-F., Huang, C.-Y., Hou, C.-W., ... Kuo, C.-H. (2012). Oral Rg1 supplementation strengthens antioxidant defense system against exercise-induced oxidative stress in rat skeletal muscles. *Journal of the International Society of Sports Nutrition*, 9(1), 23. doi: 10.1186/1550-2783-9-23

SENACTIV® ELIMINATES SENESCENT MUSCLE CELLS (2)

- Decreases SA-β-gal, a biomarker of senescent cell*
- Reverses apoptotic DNA fragmentation, a key feature of apoptosis*
- Reverses leukocyte infiltration in muscle faster*
- Increase in iNOS mRNA expression in muscle suggests an enhanced phagocytic function of macrophage*
- Increase in IL-6 mRNA expression in muscle suggests an enhanced phagocytic function of macrophage*
- Decrease in collagenase attenuated inflammatory collagenase activation*

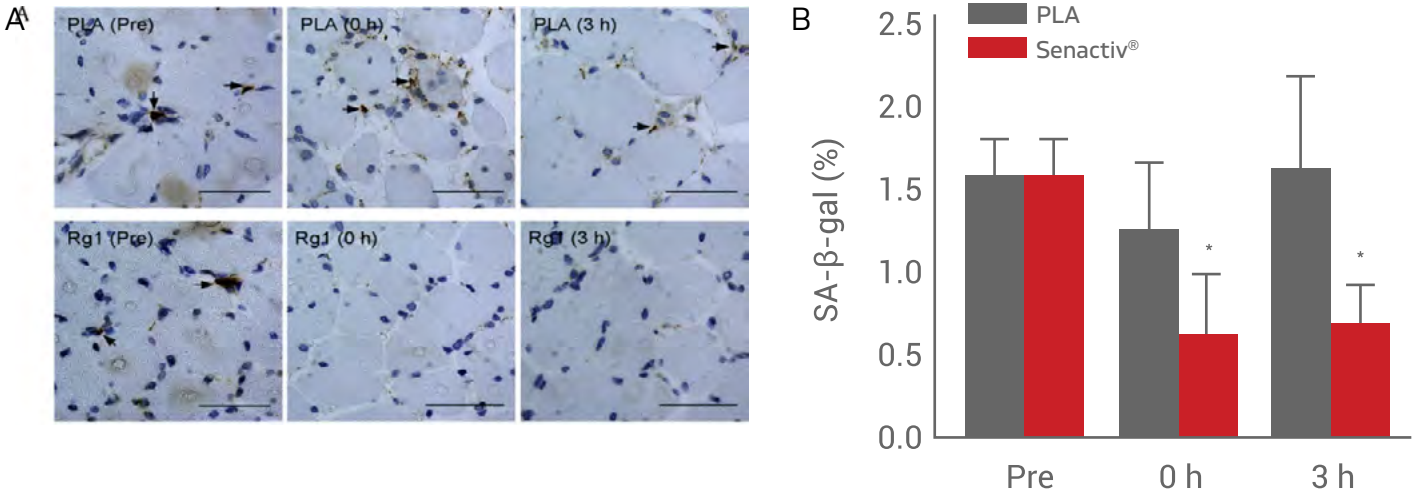
*In vastus lateralis after a 60 min cycling at 70% VO_2max

2. Wu, J., Saovieng, S., Cheng, I.-S., Liu, T., Hong, S., Lin, C.-Y., ... Kuo, C.-H. (2018). Ginsenoside Rg1 supplementation clears senescence-associated β-galactosidase in exercising human skeletal muscle. *Journal of Ginseng Research*. doi: 10.1016/j.jgr.2018.06.002

SENESCENCE-ASSOCIATED β-GALACTOSIDASE (SA-β-GAL) IN HUMAN MUSCLE AFTER EXERCISE

(A) Representative immunohistochemical staining images showing SA-β-gal (brown stain indicated by arrows) in vastus lateralis muscle of a participant.

(B) Senactiv® supplementation 1 h before exercise decreases SA-β-gal in vastus lateralis muscle after a 1 h cycling at 70% VO_2max.



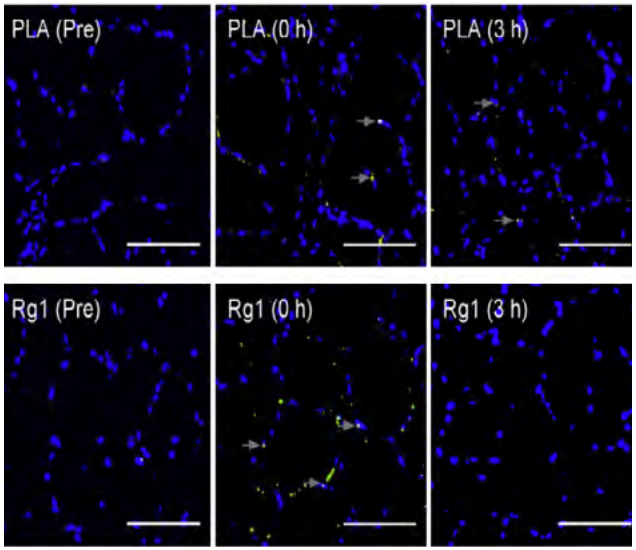
APOPTOTIC DNA FRAGMENTATION IN HUMAN MUSCLE AFTER EXERCISE

(A) Representative images for apoptotic DNA fragmentation (green, indicated by arrows) and DAPI (4,6-diamidino-2-phenylindole) nuclei (blue) in vastus lateralis muscle cross-section.

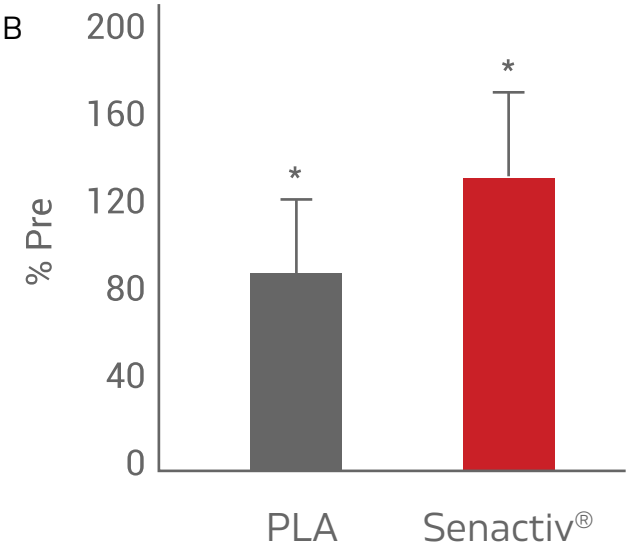
(B) Exercise increases the number of apoptotic nuclei for both PLA and Senactiv® trials.

(C) Senactiv® supplementation 1 h before exercise reverses apoptotic nuclei in vastus lateralis muscle during a 3 h recovery.

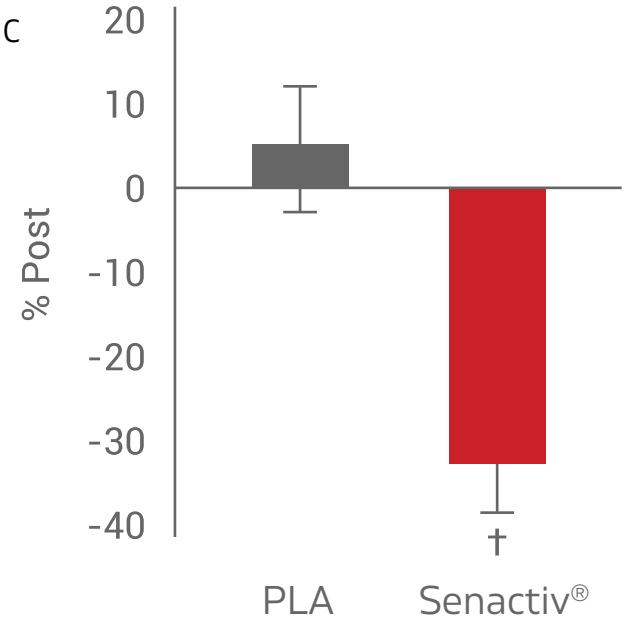
A



B



C



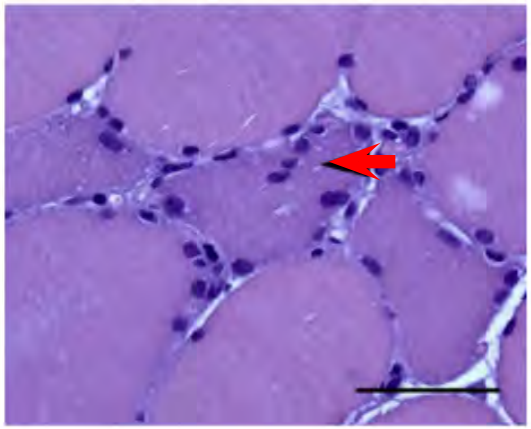
LEUKOCYTE INFILTRATION IN HUMAN MUSCLE AFTER EXERCISE

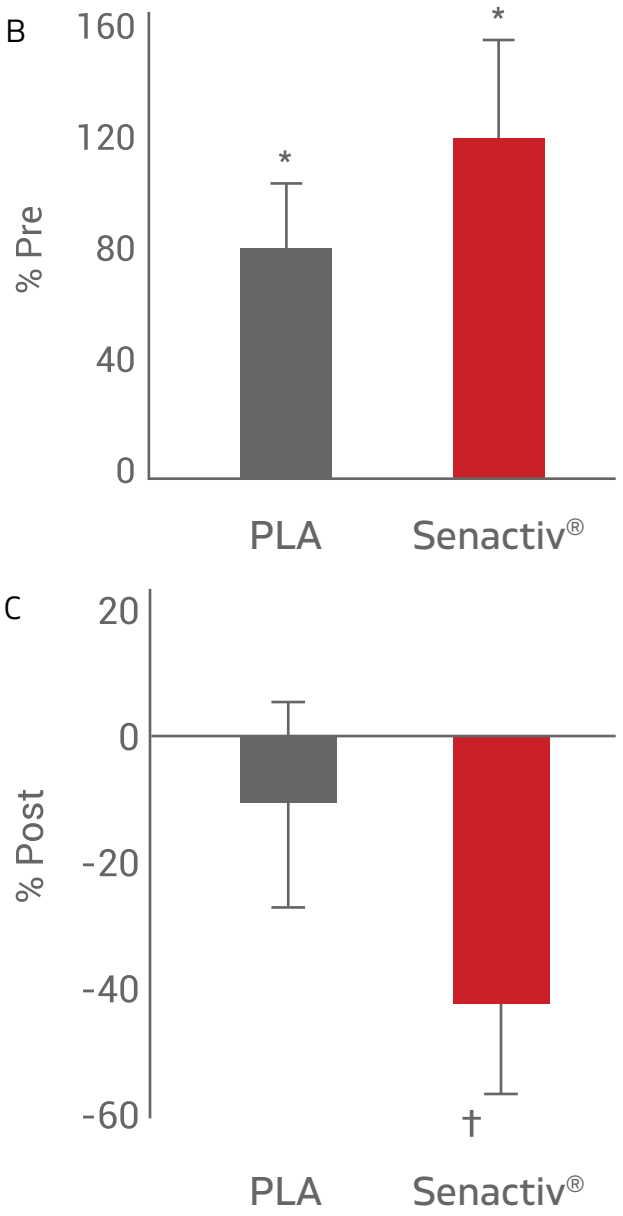
(A) Representative hematoxylin and eosin staining images showing leukocyte infiltration (arrow) in vastus lateralis muscle cross-section of a participant.

(B) Leukocyte infiltration increases after exercise in both PLA and Senactiv® trials.

(C) Leukocyte infiltration reverses faster during a 3 h recovery in the Senactiv® trial compared against the PLA trial.

A

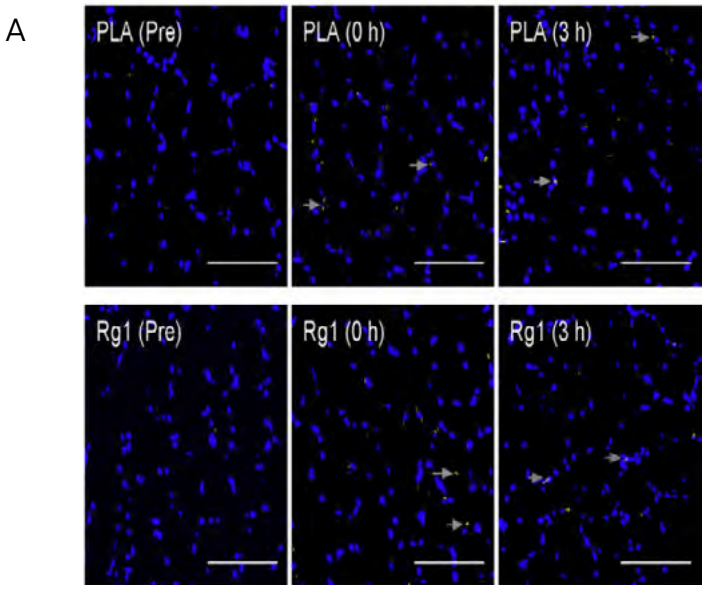


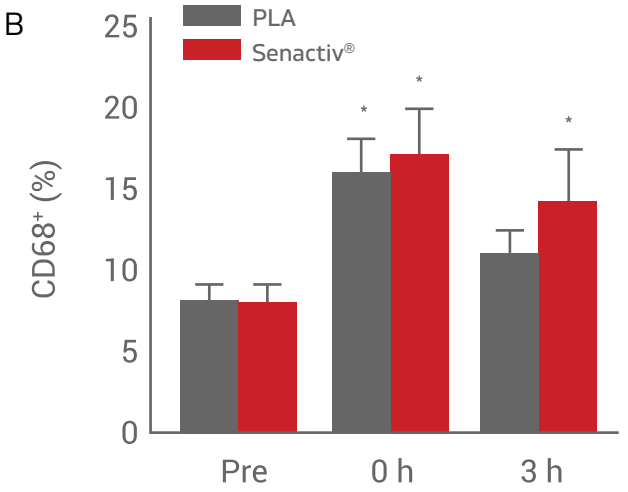


CD68+ MACROPHAGE INFILTRATION IN HUMAN MUSCLE AFTER EXERCISE

(A) Representative immunofluorescence staining images showing CD68+ cells (green) in vastus lateralis muscle cross-section.

(B) CD68+ macrophage increases after 1 h cycling at 70% VO_2max during both PLA and Senactiv® trials.



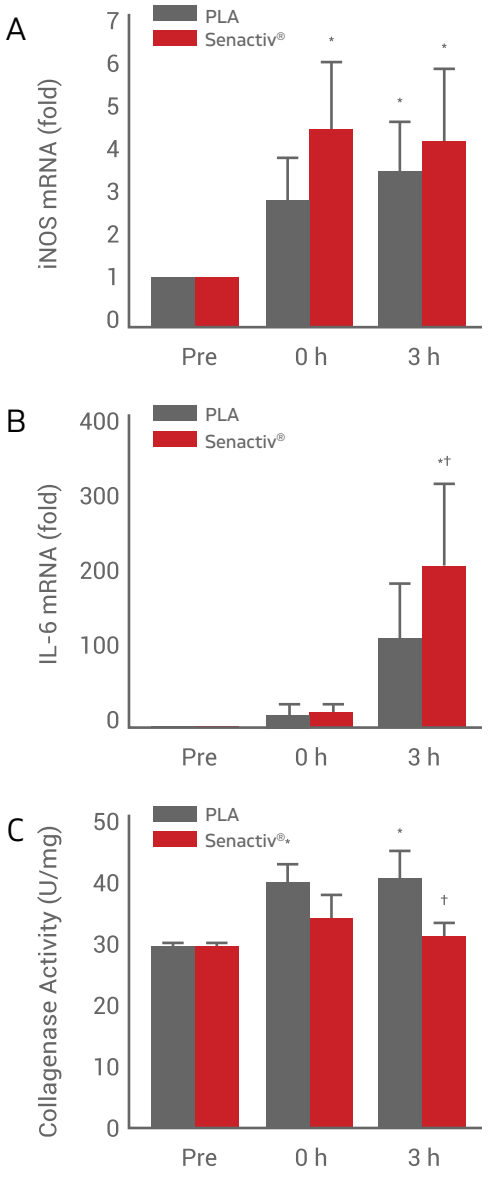


INDUCIBLE NITRATE OXIDE SYNTHASE (INOS) AND INTERLEUKIN 6 (IL-6) mRNA LEVELS IN HUMAN MUSCLE AFTER EXERCISE

(A) iNOS mRNA level in vastus lateralis shows an earlier increase during the Senactiv® trial.

(B) IL-6 mRNA level increases after exercise in both PLA and Senactiv® trials. During a 3 h recovery, this increase is further amplified, to a greater extent, for the Senactiv® trial above the PLA trial.

(C) Collagenase activity increases after exercise only in the PLA trial. Collagenase activity is lower in the Senactiv® trial, compared with the PLA trial after a 3 h post-exercise recovery.



SENACTIV® IMPROVES ENDURANCE/STAMINA AND RECOVERY BY ACCELERATING THE REPAIR AND REGENERATION OF EXERCISING SKELETAL MUSCLES

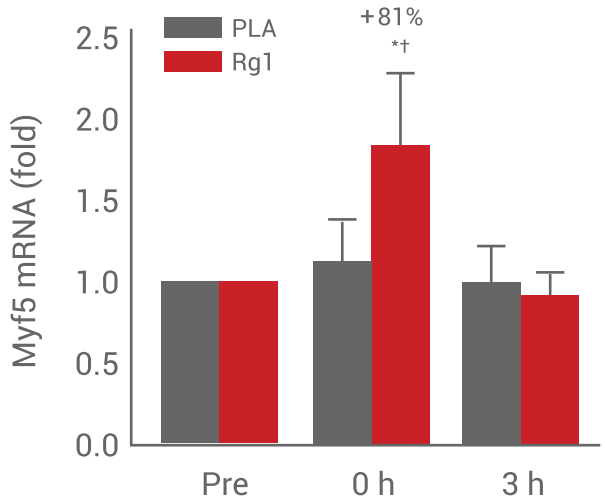
Endurance or high-intensity exercise increases muscle damage. Yet, muscle damage induces muscle repair, regeneration and growth. The key is to activate the Pax-7 and Myf5 gene expression that leads to satellite cell activation, proliferation, differentiation and nucleus fusion. Satellite cell availability determines the resilience of muscle against physical challenges.

Senactiv® was shown in a double-blind, placebo-controlled crossover human study published in the Journal of Functional Foods to increase the Pax-7 and Myf5 mRNA by 81% that leads to satellite cell activation, proliferation, differentiation and nucleus fusion into existing muscle tissue. As evidenced by the increased centrally-nucleated muscle cells. The accelerated myogenesis of exercising skeletal muscles may explain the improved high-intensity endurance performance.

5. Wu, J., Saovieng, S., Cheng, I.-S., Jensen, J., Jean, W.-H., Alkhatib, A., ... Kuo, C.-H. (2019). Satellite cells depletion in exercising human skeletal muscle is restored by ginseng component Rg1 supplementation. *Journal of Functional Foods*, 58, 27–33. doi: 10.1016/j.jff.2019.04.032

SENACTIV® INCREASES MYF5 mRNA EXPRESSION OF HUMAN SKELETAL MUSCLE IMMEDIATELY AFTER 60 MIN CYCLING (70% VO_2MAX) BY 81% (5)

Senactiv® was shown in a randomized double-blind placebo-controlled crossover human clinical trial (5) to increase the Myf5 mRNA expression by 81% immediately after a 60 min cycling exercise at 70% VO_2max. Induction of Myf5 mRNA expression is generally regarded as a hallmark for commitment of myogenesis.

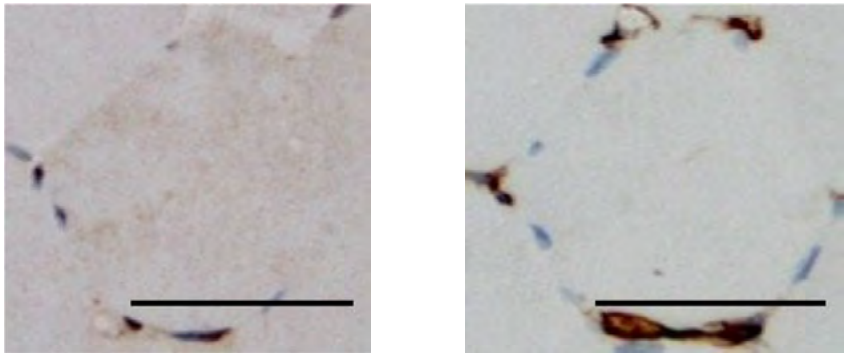


Myf5 mRNA in exercising human skeletal muscle. Expression levels are normalized to baseline (Pre). Values are expressed as means±SE (N=12). *Significantly different from baseline (Pre), P<0.05. †Significantly different from PLA, P>0.05. PLA:Placebo.

5. Wu, J., Saovieng, S., Cheng, I.-S., Jensen, J., Jean, W.-H., Alkhatib, A., ... Kuo, C.-H. (2019). Satellite cells depletion in exercising human skeletal muscle is restored by ginseng component Rg1 supplementation. *Journal of Functional Foods*, 58, 27–33. doi: 10.1016/j.jff.2019.04.032

SENACTIV® DECREASES SENESCENT CELLS AND TRIGGERS CELL RENEWAL AND GROWTH TO INCREASE PHYSICAL FITNESS AND LONGEVITY

Regular exercise improves physical fitness and lowers mortality by decreasing aged cell population in the human body, resulting in tissue renewal. Exercise triggers a brief inflammation in challenged tissues that serves as an innate mechanism to eliminate unhealthy cells followed by regeneration. A recent finding (6) of decreased $p16^{INK4a+}$ senescent cells together with $CD68^{+}$ macrophage infiltration in the human skeletal muscle after resistance exercise supports this concept. Decreased senescent cell proportion in capillaries provides benefits in physical fitness and increasing life expectancy.



a. $p16^{INK4a+}$ b. $CD34^{+}$

Senescent stem cells in capillaries surrounding myofibers of human skeletal muscle from healthy young men aged ~20 years. Representative serial immunohistochemical staining image *a* indicates that the detected senescent cells ($p16^{INK4a+}$) are mostly stem cells ($CD34^{+}$). Image *B* located in capillaries of human skeletal muscle.

6. Kuo, C.-H. (2019). Exercise Against Aging: Darwinian Natural Selection Among Fit and Unfit Cells Inside Human Body. *Journal of Science in Sport and Exercise*, 1(1), 54–58. doi: 10.1007/s42978-019-0002-y

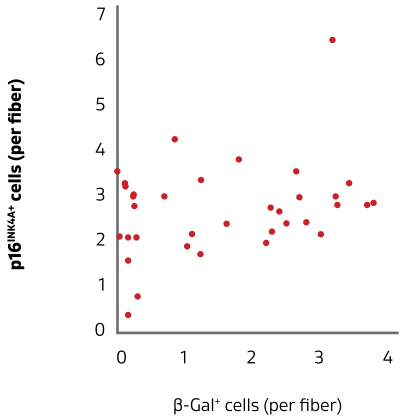
SENACTIV® POTENTIATES THE INFLAMMATION RESPONSE (PRE-CONDITIONING) & RESULTS IN AN EARLY RESOLUTION OF THE EXERCISE STRESS RESPONSE

A recent study published in the journal, *Aging* (7), demonstrates Senactiv® promoting a protective mechanism for maintaining genetic stability of replicable cells against aerobic exercise.*

$p16^{INK4a}$ is a cellular senescence and oxidative stress-sensitive protein that is only detected in senescent cells. $p16^{INK4a}$ induces macrophage phagocytosis to clear senescent cells in muscle and stimulates tissue repair during inflammation.

Senactiv® has shown in a 60 minute 70% VO_2max cycling exercise human trial to reverse $p16^{INK4a}$ near to baseline 3 h after the exercise compared to +21-fold increase in the placebo group. The reversal of $p16^{INK4a}$ indicates the clearance of senescent cells (7).

Senactiv® also decreases IL-10 mRNA, an anti-inflammatory biomarker, 3-fold 3 h after exercise, indicating the cease of macrophage phagocytosis or the absence of senescent cells after the exercise (7).



7. Kuo, et al. (2020). Aerobic exercise induces tumor suppressor p16ink4a expression of endothelial progenitor cells in human skeletal muscle. *Aging* 12(16).

SENACTIV® IS GRAS/NDI SELF-AFFIRMED

Senactiv® received US GRAS/NDI self-affirmation in April, 2015 from AIBMR, Washington, USA. The affirmation was based on the 28-day Repeated Oral Dose Toxicity Study in Rats completed in December, 2014 by TOXI-COOP ZRT. The NOAEL (No Observed Adverse Effect Level) is 600 mg/kg bw/day, and many toxicity studies on *Panax notoginseng* and *Rosa roxburghii* in published papers.

VIEW SCIENTIFIC PAPERS

VIEW SCIENTIFIC PAPERS

Hou, C.-W., Lee, S.-D., Kao, C.-L., Cheng, I.-S., Lin, Y.-N., Chuang, S.-J., ... Kuo, C.-H. (2015). Improved inflammatory balance of human skeletal muscle during exercise after supplementations of the ginseng-based steroid Rg1. *Plos One*, 10(1). doi: 10.1371/journal.pone.0116387

Korivi, M., Hou, C.-W., Huang, C.-Y., Lee, S.-D., Hsu, M.-F., Yu, S.-H., ... Kuo, C.-H. (2012). Ginsenoside-Rg1 protects the liver against exhaustive exercise-induced oxidative stress in rats. *Evidence-Based Complementary and Alternative Medicine*, 2012, 1–8. doi: 10.1155/2012/932165

Kuo, C.-H. (2019). Exercise against aging: Darwinian natural selection among fit and unfit cells inside human body. *Journal of Science in Sport and Exercise*, 1(1), 54–58. doi: 10.1007/s42978-019-0002-y

Wu, J., Saovieng, S., Cheng, I.-S., Liu, T., Hong, S., Lin, C.-Y., ... Kuo, C.-H. (2018). Ginsenoside Rg1 supplementation clears senescence-associated β-galactosidase in exercising human skeletal muscle. *Journal of Ginseng Research*. doi: 10.1016/j.jgr.2018.06.002

Wu, J., Saovieng, S., Cheng, I.-S., Jensen, J., Jean, W.-H., Alkhatib, A., ... Kuo, C.-H. (2019). Satellite cells depletion in exercising human skeletal muscle is restored by ginseng component Rg1 supplementation. *Journal of Functional Foods*, 58, 27–33. doi: 10.1016/j.jff.2019.04.032

Yu, S.-H., Huang, H.-Y., Korivi, M., Hsu, M.-F., Huang, C.-Y., Hou, C.-W., ... Kuo, C.-H. (2012). Oral Rg1 supplementation strengthens antioxidant defense system against exercise-induced oxidative stress in rat skeletal muscles. *Journal of the International Society of Sports Nutrition*, 9(1), 23. doi: 10.1186/1550-2783-9-23

Kuo, et al. (2020). Aerobic exercise induces tumor suppressor p16ink4a expression of endothelial progenitor cells in human skeletal muscle. *Aging* 12(16).

For questions and additional information please contact

NuLivScience

nulivscience.com