PLT
HEALTH SOLUTIONS

RipFACTOR®
MUSCLE ACCELERATOR

RipFACTOR® Muscle Accelerator
Scientific Summary

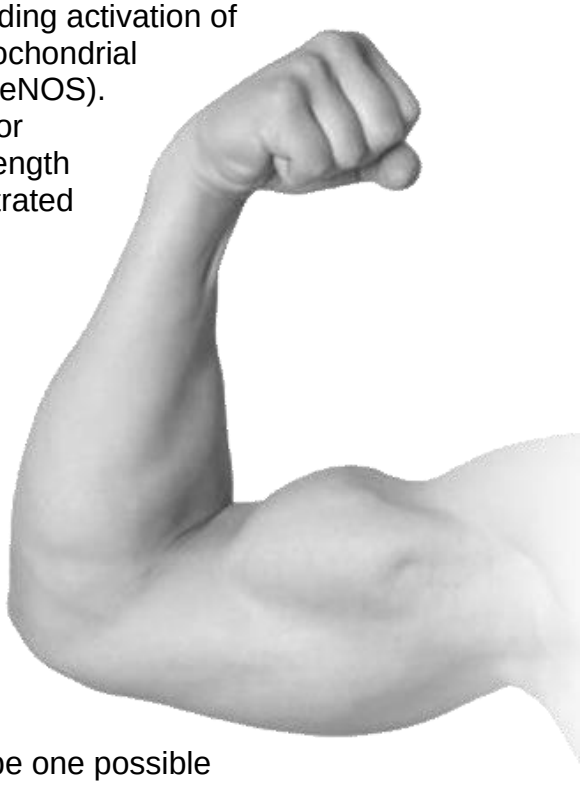
Two clinical studies support strength, endurance, muscle & testosterone messaging

Three lines of evidence:

Increased Endurace | Enhanced Strength | Muscle Growth

INTRODUCTION

The novel botanical combination, LI12542F6 (sold commercially as RipFACTOR®, MyoTOR®, and RipForce®) is a clinically researched dietary ingredient for support of muscle building. Preclinical studies show that LI12542F6 (hereafter referred to as RipFACTOR) works via multiple mechanisms of action, including activation of mTOR, catabolic inhibition (20S proteasome), increased mitochondrial metabolism and increased endothelial nitric oxide synthase (eNOS). These activities support blood flow and anabolism required for muscle building and translate to increased muscle mass, strength and endurance among other effects that have been demonstrated in two randomized, double-blind clinical trials.



DEVELOPMENT

While conducting a clinical trial on a composition containing *S. indicus*, researchers at Laila Nutraceuticals R&D Center in Vijayawada, India, observed increased energy levels and physical activity from many study subjects. This observation prompted their team of taxonomists and ethnobotanists to survey traditional Ayurvedic texts and literature for corroboration. The literature confirmed traditional use of *S. indicus* for rejuvenation, increase of physical strength, muscle growth, intelligence, and longevity.

Activation of endothelial nitric oxide (eNOS) was thought to be one possible mechanism to explain these effects, since it enhances mitochondrial function and mitochondrial biogenesis, and thus helps to improve strength and endurance. Laila's researchers studied *S. indicus* in vitro for eNOS-induced nitric oxide (NO) production and confirmed activity. Following an exhaustive search for a complementary second ingredient, they chose *Mangifera indica*, due to the many complementary activities of its main active constituent, mangiferin, a xanthone.*S. indicus* and *M. indica* extracts were combined in different ratios, and the compositions thus obtained were evaluated again in various cellular models described below. One blend in particular (LI12542F6), comprising two parts *S. indicus* and one part *M. indica*, showed synergy and was selected for further development.

Sphaeranthus indicus: Commonly known as East Indian Globe Thistle, Gorakhmundi, or Bodatharam, *Sphaeranthus indicus* is an aromatic herb distributed widely in plains throughout India (Ramachandran, 2013),[1] with a long and varied history of use in the Ayurvedic medicine tradition. Individual parts or the plant in its entirety are used for managing a variety of ailments owing to a multitude of reported functions. Most notable are immunomodulatory, hepatoprotective, analgesic, anti-diabetic, antioxidant, anxiolytic, anti-inflammatory and antihyperlipidemic activities, among many other uses.[2]

Mangifera indica: *Mangifera indica* (mango tree) is a native plant of the Indian subcontinent that is now naturalized in many tropical regions across the globe.[3] It has been cultivated in India for as long as 4,000 to 6000 years. It has been used in China since the 7th Century; in East Africa since the 10th Century AD; in the Philippines since the beginning of the 15th Century. Its known use in the United States dates the second half of the 19th Century.[4]

Mango tree bark preparations have been used widely as folk medicines in tropical and subtropical regions.[5] Mangiferin, a glucosyl xanthone found in mango fruit, leaves, and bark, has been reported to have antioxidant,[6] antidiabetic, immunomodulatory, antigenotoxic, and anti-inflammatory properties.[7] The bark and leaves of *M. indica* are rich in mangiferin,[8] with the bark containing approximately 20% mangiferin, whereas the leaf extract contains around 7% mangiferin.[9]

As mentioned previously, vasodilatory activity of *Sphaeranthus indicus* was an early research target and a consideration in the search for complementary botanical for the original formula. Like *S. indicus*, *Mangifera indica* is also vasodilatory, as well as having a documented traditional use of regulating blood pressure[10] [11], likely via ACE inhibition.[12]

In 2020, a new form of the ingredient was introduced – RipFACTOR WD – which is a neutral tasting, water-dispersible version of the original ingredient for use in taste-sensitive applications and a broader range of delivery systems.

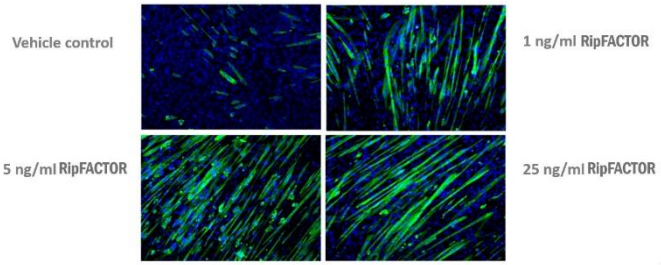
PRECLINICAL RESEARCH

It is beyond the scope of this paper to comprehensively review the research on *Sphaeranthus* and *Mangifera*; many excellent reviews are available and are cited in the references. Selected activities are of special interest regarding RipFACTOR and the formula itself has been studied in preclinical and clinical settings. That research is reviewed here.

1. **ROS inhibition**: RipFACTOR was studied in vitro to determine its capacity to inhibit generation of Reactive Oxygen Species (ROS).[13] In comparison with other herbal extracts and a green tea positive control, 5µg/mL of RipFACTOR (formulation containing no excipients) exhibited synergistic efficacy in inhibiting ROS generation in Phorbol 12-myristate 13-acetate (PMA)-induced HL-60 human monocytic cells.
2. **Nitrite induction**: RipFACTOR was studied *in vitro* to determine its capacity to modulate nitrite production.[14] In comparison with the individual ingredients, the RipFACTOR combination exhibited synergistic induction of nitrite production in human endothelial cells (EAhy926).
3. **Inhibition of NADPH Oxidase**: RipFACTOR was studied *in vitro* to assess its inhibition of NADPH Oxidase (NOX) activity**.**[15] The combination exhibited strong

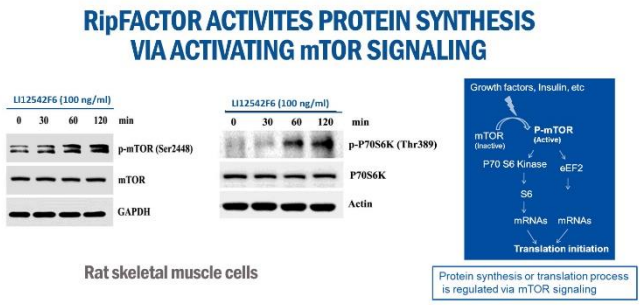
inhibition of NOX with an IC50 of 261.014 ng/ml, i.e., it is a “strong antioxidant,” according to the researchers.

4. **Myoblast cell proliferation:** Myoblasts are embryonic precursors of myocytes (muscle cells). To estimate if RipFACTOR modulates myoblast cell proliferation, researchers conducted two independent tests.[16] They confirmed that the herbal combination induced cell proliferation in L6 rat skeletal myoblasts.
5. **Myoblast cellular protein**: Researchers assessed the extent to which RipFACTOR influences total cellular proteins in muscle cells**.**[17] Under the test conditions, RipFACTOR dose-dependently induced total protein content in L6 rat skeletal myoblasts.
6. **Myotube formation**: Researchers evaluated the capacity of RipFACTOR to stimulate myotube formation in C2C12 cell line.[18] In the study, RipFACTOR induced myotube formation in mouse myoblast cells. The stimulation of myotube formation is evident in a progressive series of phase contrast and immuno-fluorescence images.



Immunofluorescence images showing RipFACTOR increase in Myosin Heavy Chain protein expression in C2C12 myotubes.

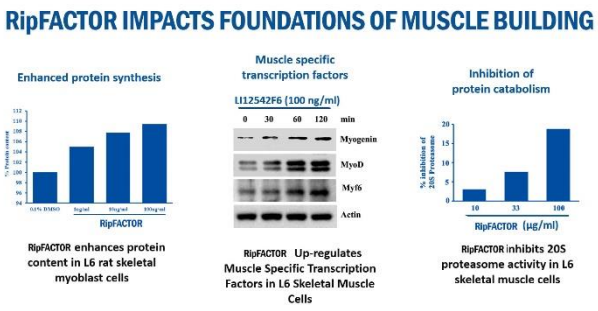
7. **mTOR activation**: The effect of RipFACTOR on different muscle markers in rat skeletal muscle cells was assessed.[19]
    a. RipFACTOR was found to increase phosphorylation of mTOR at ser2448, indicating activation of mTOR pathway in L6 rat skeletal muscle cells.
    b. RipFACTOR was found to hyper-phosphorylate P70S6K at Thr389, indicating activation of P70S6K, which validates activation of mTOR pathway in L6 rat skeletal muscle cells.
    c. RipFACTOR was found to trigger upregulation of key myogenic transcription factors (such as Myogenin, MyoO, Myf6) in rat skeletal muscle cells.



Together, these observations suggest that RipFACTOR activates ribosomal protein synthesis machinery via activation of the mTOR pathway; and also stimulates key myogenic (muscle-building) factors. These observations provide a molecular basis of muscle mass enhancing effect of RipFACTOR.

8. **Mitochondrial biogenesis activation**: Researchers evaluated the mitochondrial biogenesis activating capacity of RipFACTOR.[20] RipFACTOR significantly induced mitochondrial biogenesis in L6 rat skeletal myoblast cells. These results led the researchers to conclude that the combination is a good candidate for preventing muscle loss.

9. **Mitochondrial OX-PHOS proteins**: The effect of RipFACTOR on modulating key mitochondrial oxidative phosphorylation (OX-PHOS) proteins was investigated using an L6 rat skeletal myoblast model.[21] Representative immunoblot images depict that RipFACTOR up-regulates protein expression of ATP summary synthase and cytochrome C oxidase 1 (COX-1) in L6 rat myoblast cells. Interpretation of these results is that RipFACTOR activated mitochondrial function via inducing key OX-PHOS proteins in L6 rat myoblast cells.
10. **Mitochondrial membrane potential**: The mitochondrial membrane potential (ΔΨm) results from redox transformations associated with the activity of the citric acid cycle and is an intermediate form of energy storage used by the enzyme ATP synthase to make ATP. Maintaining stable ΔΨm and levels of intracellular ATP is considered requisite for normal cell functioning.[22] Researchers evaluated the efficacy of RipFACTOR in stabilizing ΔΨm.[23] Using a hydrogen peroxide-induced L6 rat skeletal myoblast model, they found that RipFACTOR stimulated significant recovery from mitochondrial membrane depolarization in oxidative stress- induced L6 rat skeletal myoblasts.



11. **20S proteasome inhibition:** The proteasome is a large protein complex responsible for degradation of intracellular proteins. It is made up of two subcomplexes: a catalytic core particle (also known as the 20S proteasome) and one or two terminal 19S regulatory particles that serve as a proteasome activator.[24] The 20S proteasome inhibiting capacity of RipFACTOR was assessed in an experimental L6 rat myoblast cell line,[25] to assess its capacity for preventing degradation of skeletal muscle cells. The combination significantly inhibited 20S proteasome activity. EGCG was used as positive control.
12. **Testosterone activation**: MA-1O mouse Leydig cells were used to determine if RipFACTOR would activate testosterone production capacity.[26] RipFACTOR produced dose-dependent increase of testosterone production under the experimental conditions.

IN VIVO TESTS

Endurance: Researchers evaluated the efficacy of RipFACTOR to affect energy endurance potential in Swiss albino mice.[27] Using a forced swim test model, mice in the RipFACTOR group had increases in slow swim time, fast swim time, distance traveled, and average velocity, i.e., the formula improved energy endurance potential in the forced swim test compared to control.

Muscle atrophy: In a 28-day preclinical study, researchers evaluated RipFACTOR to determine if supplementation would alleviate muscle loss and improve muscle strength in dexamethasone-induced (DEX) Sprague Dawley rats.[28] Rats were randomized into four groups and dosed with vehicle/test items/reference for 29 days. From day 8 to 28, dexamethasone (0.05 mg/kg; i.p.) was administered to all animals except vehicle

control. Forelimb grip strength was measured on day 29. At the end of the study, the RipFACTOR-supplemented rats showed less weight loss in comparison with the DEX-induced rats. Increased strength (grip) and increased muscle weight was observed in the supplemented group.

Atrogin-1 and Murf-1 are the key molecular proteins in ubiquitin proteasome pathway, which controls protein degradation when activated in sarcopenia and muscle wasting. In this study, Atrogin-1 and Murf-1 expressions in gastrocnemius muscle were normalized. This observation suggests that RipFACTOR modulates the ubiquitin proteasome pathway. Supplementation also improved mTOR activation in the skeletal muscle, suggesting that RipFACTOR promotes protein synthesis in the muscles at the ribosomal level. Together, these observations might explain the basis of reduced muscle loss and improved muscle strength in glucocorticoid-induced atrophied rats.

CLINICAL TRIALS

In two double-blind clinical trials, subjects taking RipFACTOR had highly significant improvements in muscle endurance, strength, muscle size, and lean body mass compared to placebo. These effects were observed in both resistance-trained healthy men and in untrained men performing bench press, cable pull-down, leg press, and dynamometer (grip strength) tests. Statistically significant improvements are documented after just two weeks and continue to improve throughout the length of the 2-month studies.

The two trials were both 8 weeks long, with subjects evaluated in the gym 3 times per week. However, there are also some important distinctions between the two studies:

- Men in Study 1 were recreationally active and at least familiar with resistance training, whereas those in Study 2 were recreationally active but resistance training-naive. The training protocol was supervised in both studies, but more closely in Study 2 to ensure proper training was followed in this group of resistance-training naïve participants.
- The training protocol for Study 1 involved whole-body training (bench press, leg press, cable pull-down, treadmill, dynamometer) whereas in Study 2 participants

were trained only on the measured endpoints (one set of bilateral bench press and leg extension resistance training sessions).

- Study 1 was conducted using RipFACTOR at 650 mg/d (Ultra-Performance dose). Study 2 used RipFACTOR WD at two doses: 425 mg (Performance dose) and 850 mg/d (Ultra-Performance dose). Both the 650 mg and 850 mg doses of RipFACTOR and RipFACTOR WD, respectively, contained the same amount of actives (650 mg); the only difference was 200 mg of excipient in the 850 mg dose. The 425 mg dose of WD contained 325 mg of actives and 100 mg of excipient.

Standard	Water-Dispersible
325 mg/d	425 mg/d**

Standard	Water-Dispersible
650 mg/d*	850 mg/d**

* Dose used in Study 1
** Dose used in Study 2

Study 1 evaluated the efficacy of RipFACTOR to improve muscle health. In a randomized, double-blind, placebo-controlled trial, 40 male participants of 18–40 yrs age were assigned to receive 650 mg of RipFACTOR (A) or Placebo (P) for 56 days.[29] The primary endpoint was change from baseline in muscle strength, assessed by 1-RM Bench and Leg presses. Secondary endpoints included muscle endurance, time to exhaustion,muscle size, body composition and free testosterone. Safety was also assessed. **Results**: Significant ($P < 0.0001$) increases in change from baseline for strength bench and leg presses and grip strength were observed in the A vs. P group beginning at 14 d and continuing throughout the study. Muscle endurance and time to exhaustion were similarly increased by 14 d and continued for the remainder of the study. By day 56, the mid-upper arm circumference was statistically increased in A vs. P ($P < 0.05$) in left and right arms. Secondary endpoints including muscle endurance, TTE, body composition, and free testosterone were all significantly improved compared to placebo. Serum Cortisol was significantly lower in the treatment group compared to placebo. Lean body mass (the difference between total body weight and body fat weight) increased by 1.44 kg (2.8% improvement) in the RipFACTOR group compared to just 0.03 kg (0.06% improvement) in the placebo group. Total Body Fat decreased by 0.97 kg (5.25% decrease) in the RipFACTOR group and by 0.20 kg (1.15% decrease) in the placebo group. Percent Body Fat decreased by 1.50% in the RipFACTOR group compared with only 0.24% in the placebo group.

Study 2 evaluated the efficacy of RipFACTOR WD to improve muscle health.[30] This was a prospective, randomized, double-blind, placebo-controlled study to assess the comparative efficacy and safety of RipFACTOR WD 425 mg/d (Group A, “Performance dose”) and RipFACTOR WD 850 mg/d (Group B, “Ultra-Performance dose”) in comparison with two groups consuming placebo and performing either one set of physical training (Group C) or two sets of training (Group D), respectively. **Results**: 1RM bench press values increased by 37% and 44% in treatment groups A and B respectively, versus 17% and 24% in placebo groups C and D respectively, from

baseline to the end of the study. Significant improvement in 1RM leg extension values was observed after 14 days of supplementation in treatment groups A and B when compared to placebo group C. Statistically significant increase in 1RM values of leg extension was observed in the treatment groups A and B when compared with both placebo groups C & D (at days 28 and 56). Muscle endurance, measured as number of reps on bench press, was also different between active and placebo groups (A-C, B-D, and B-D achieved statistical significance). Both Free and Total Testosterone were significantly increased comparing Groups A-C and Groups B-C. Both doses of RipFACTOR improved physical strength in training-naïve subjects as measured by bench press and leg extension. However, 850 mg/d was more efficacious in enhancing the physical endurance of the subjects compared to 425 mg/d.

Comparing the two doses

Two doses of RipFACTOR have been shown to support muscle building:

- The “Performance” dose is 325 mg/d (standard) or 425 mg/d (water-dispersible), both providing the same amounts of actives. The water-dispersible form was used in the second clinical study.
- The “Ultra-Performance” dose is 650 mg/d (standard) or 850 mg/d (water-dispersible), both providing the same amounts of actives. The standard form was used in the first clinical study; the water-dispersible form was used in the second clinical study.

Muscle Strength Comparison

1-RM Bench Press: Both doses produced greater than twice the improvement of placebo. Both doses were as efective as doubling exercise (at 2, 4, and 8 weeks); the Ultra dose was more effective than doubling exercise (at 4 and 8 weeks).

- Study 1: Ultra: increased 27.60 kg; Placebo: increased 4.95 kg.
    - ANCOVA (analysis of covariance) Assessment: The difference was statistically significant ($p<0.0001$).
- Study 2: Perf: increased 19.42 kg; Ultra: increased 22.6 kg; Placebo 1: increased 8.8 kg; Placebo 2: increased 12.61 kg.
    - ANCOVA Assessment: The difference between the Performance dose and Placebo 1 was significant ($p=0.0031$); the difference between the Performance dose and Placebo 2 was not significant ($p=0.121$); the difference between the Ultra dose and Placebo 1 was significant ($p<0.001$); the difference between the Ultra dose and Placebo 2 was significant ($p=0.0086$)

1-RM Leg Press

- Study 1: Ultra: increased 29.45 kg; Placebo: increased 5.7 kg
    - ANCOVA Assessment: The difference was statistically significant ($p<0.0001$).

1-RM Leg Extension: Both doses produced greater than twice the improvement of placebo. Both doses were more effective than doubling exercise (at 4 and 8 weeks).

- Study 2: Perf: increased 16.92 kg; Ultra: increased 19.4 kg; Placebo 1: increased 8.4 kg; Placebo 2: increased 11.52 kg
    - ANCOVA Assessment: The difference between the Performance dose and Placebo 1 was significant ($p=0.0013$); the difference between the Performance dose and Placebo 2 was significant ($p=0.0343$); the difference between the Ultra dose and Placebo 1 was significant ($p=0.0001$); the difference between the Ultra dose and Placebo 2 was significant ($p=0.0044$)

Grip strength (Dynamometer): Only the Ultra-Performance dose was studied. Greater gains than placebo at 2, 4, 8 weeks.

- Study 1: Ultra: increased 13.60 kg; Placebo: increased 10.60 kg
    - ANCOVA Assessment: The difference was statistically significant ($p=0.0006$).

Muscle Size Comparison

Arm circumference: Only the Ultra-Performance dose was studied.

- Study 1:
    - Left bicep: Ultra: increased 0.48 cm; Placebo: increased 0.15 cm
        - ANCOVA Assessment: The difference was statistically significant ($p=0.0429$)
    - Right bicep: Ultra: increased 0.45 cm; Placebo: increased 0.11 cm
        - ANCOVA Assessment: The difference was statistically significant ($p=0.0427$)

Muscle Endurance Comparison

Cable pulldown reps: Only the Ultra-Performance dose was studied. Greater gains than placebo were seen at 2,4, and 8 weeks.

- Study 1: Ultra: Increase of 5.1 reps; Placebo: increase of 2.6 reps
    - ANCOVA Assessment: The difference was statistically significant ($p<0.0001$)

Bench press reps: Both doses produced greater improvement than placebo at 8 weeks. Both doses were as effective as doubling exercise (at 2, 4, and 8 weeks); the Ultra-Performance dose was more effective than doubling exercise (at 8 weeks).

- Study 2: Perf: Increase of 6.69 reps; Ultra: Increase of 7.36 reps; Placebo 1: Increase of 4.68 reps; Placebo 2: Increase of 4.82 reps
    - ANCOVA Assessment: The difference between the Performance dose and Placebo 1 was significant ($p=0.0432$); the difference between the Performance dose and Placebo 2 was significant ($p=0.078$); the difference between the Ultra dose and Placebo 1 was significant ($p=0.0041$); the difference between the Ultra dose and Placebo 2 was significant ($p=0.0091$)

Leg extension reps: Both doses produced greater improvement than placebo at 8 weeks. Both doses were as effective as doubling exercise (at 2, 4, and 8 weeks); the Ultra-Performance dose was more effective than doubling exercise (at 8 weeks).

- Study 2: Perf: Increase of 7.54 reps; Ultra: Increase of 8.36 reps; Placebo 1: Increase of 5 reps; Placebo 2: Increase of 6.13 reps
    - ANCOVA Assessment: The difference between the Performance dose and Placebo 1 was significant ($p=0.0038$); the difference between the Performance dose and Placebo 2 was not significant ($p=0.1443$); the difference between the Ultra dose and Placebo 1 was significant ($p=0.0011$); the difference between the Ultra dose and Placebo 2 was significant ($p=0.05$)

Cardio Endurance Comparison

Time to exhaustion: Only the Ultra-Performance dose was studied. Greater improvement compared to placebo was seen at 2, 4, and 8 weeks

- Study 1: Ultra: Increase by 4.82 min; Placebo: Increased by 2.32 min
    - ANCOVA Assessment: The difference was statistically significant (p=0.0008)

Biomarkers Comparison

Free testosterone: Compared to placebo, both doses statistically significantly improved Free T at 8 weeks.

- Study 1: Ultra: +3.16 pg/mL; Placebo: -1.13 pg/mL
    - ANCOVA Assessment: The difference was statistically significant (p= 0.0128)
- Study 2: Perf: +0.49 ng/dL; Ultra: +0.74 ng/dL; Placebo 1: +0.2 ng/dL; Placebo 2: +0.25 ng/dL
    - ANCOVA Assessment: The difference between the Performance dose and Placebo 1 was significant (p=0.0336); the difference between the Performance dose and Placebo 2 was not significant (p=0.0706); the difference between the Ultra-Performance dose and Placebo 1 was significant (p=0.0338); the difference between the Ultra dose and Placebo 2 was not significant (p=0.07)

Total testosterone: Compared to placebo, both doses statistically significantly improved Total T at 8 weeks.

- Study 2: Perf: +0.93 ng/dL; Ultra: +1.11 ng/dL; Placebo 1: +0.15 ng/dL; Placebo 2: +0.24 ng/dL
    - ANCOVA Assessment: The difference between the Performance dose and Placebo 1 was significant (p=0.0389); the difference between the Performance dose and Placebo 2 was not significant (p=0.1482); the difference between the Ultra-Performance dose and Placebo 1 was significant (p=0.012); the difference between the Ultra-Performance dose and Placebo 2 was not significant (p=0.0578), but trended very close to significance.

Cortisol: Ultra-Performance dose statistically significantly improved cortisol compared to Placebo at 8 weeks in first study. In the second study, this did not reach statistical significance.

- Study 1: Ultra: -36.96 pg/mL; Placebo: -6.50 pg/mL
    - ANCOVA Assessment: The difference was statistically significant (p=0.0469)

- Study 2: Perf: -0.92 mcg/dL; Ultra: -1.37 mcg/dL; Placebo 1: + 0.78 mcg/dL; Placebo 2: + 1.26 mcg/dL
    - ANCOVA Assessment: The difference between the Performance dose and Placebo 1 was not significant (p=0.1251); the difference between the Performance dose and Placebo 2 was not significant (p=0.0573), but trended close to significance; the difference between the Ultra-Performance dose and Placebo 1 was not significant (p=0.0643); the difference between the Ultra dose and Placebo 2 was significant (p=0.0272)

Free T-Cortisol ratio: Compared to placebo, both doses statistically significantly improved the Testosterone:Cortisol ratio at 8 weeks.

- Study 1 (T/C): Ultra: +0.030 ng/mL; Placebo: +0.004 ng/mL
    - ANCOVA Assessment: The difference was statistically significant (p=0.0469)
- Study 2 (C/T): Perf: -1627; Ultra: -1397; Placebo 1: -374; Placebo 2: -52
    - ANCOVA Assessment: The difference between the Performance dose and Placebo 1 was significant (p= 0.0256); the difference between the Performance dose and Placebo 2 was significant (p= 0.0158); the difference between the Ultra-Performance dose and Placebo 1 was significant (p=0.0432); the difference between the Ultra-Performance dose and Placebo 2 was significant (p=0.0283)

Body Composition Comparison

Lean body mass: Only the Ultra-Performance dose was studied. 48 times greater improvement than placebo was seen at 8 weeks.

- Study 1: Ultra: +1.44 kg; Placebo: +0.03 kg
    - ANCOVA Assessment: The difference was statistically significant (p=0.0410)

Total body fat: Only the Ultra-Performance dose was studied. Greater improvement than placebo was seen at 8 weeks.

- Study 1: Ultra: -0.97 kg; Placebo: -0.20 kg
    - ANCOVA Assessment: The difference was statistically significant (p=0.0338)

% body fat: Only the Ultra-Performance dose was studied. Greater improvement than placebo was seen at 8 weeks.

- Study 1: Ultra: -1.50%; Placebo: -0.24%

- ANCOVA Assessment: The difference was statistically significant (p=0.0172)

SAFETY AND TOXICITY

A full complement of *in vitro* and *in vivo* toxicity studies were conducted to evaluate safety of RipFACTOR. It was evaluated for mutagenicity in bacteria, clastogenicity in mouse bone marrow, acute oral and dermal toxicity in the rat, irritation (dermal, eye) in rabbit, and subacute and subchronic toxicity (28 and 90 days) in the rat.[31] All studies followed standard OECD test protocols, in accordance with the principles of Good Laboratory Practice (GLP). RipFACTOR did not induce mutations in the bacterial assay using *Salmonella* and *Escherichia coli* strains, nor did it induce genotoxic effects in erythrocytes from mouse bone marrow. RipFACTOR was found to have oral and dermal LD50 values greater than the limit dose of 2,000 mg/kg body weight in the rat. In an eye irritation/corrosion test, RipFACTOR caused conjunctival redness, corneal opacity, and chemosis and is classified as Category 2A ("irritating to eyes – reversible eye effect"). Doses in the 28-day and 90-day rat oral toxicity studies were 0, 500, 1,000, and 1,500 and 0, 1,000, 1,500, and 2,000 mg/kg body weight/day, respectively, administered by gavage. Both studies featured a recovery period. Minor effects were random and not treatment related except for local irritation of the forestomach in the 28-day study, evidenced by histopathologic examination, in mid-and high-dose animals. The frequency and severity of these effects were reduced in the recovery group; irritation as not found in the forestomach of rats in the 90-day study. The no observed adverse effect level (NOAEL) was greater than the highest dose tested, that is, >2,000 mg/kg in the 90-day study.

RipFACTOR is generally recognized as safe (GRAS) (independently confirmed).[32]

Recommended use levels

RipFACTOR is available in two forms: standard and water-dispersible (WD), both clinically evaluated and shown to be effective at two dose levels:

- Performance: 325 mg/d (standard); 425 mg/d (water-dispersible)
- Ultra-Performance: 650 mg/d (standard); 850 mg/d (water-dispersible)

REFERENCES

[1] Ramachandran S. Review on *Sphaeranthus indicus* Linn. (Koṭṭaikkarantai). *Pharmacogn Rev*. 2013;7(14):157-169. doi:10.4103/0973-7847.120517

[2] Galani VJ, Patel BG, Rana DG. *Sphaeranthus indicus* Linn.: A phytopharmacological review. *Int J Ayurveda Res*. 2010;1(4):247-253. doi:10.4103/0974-7788.76790

[3] Batool N, Ilyas N, Shabir S, Saeed M, Mazhar R. Mini-Review- A mini-review of therapeutic potential of *Mangifera indica* L. *Pak J Pharm Sci*. 2018;31(4):1441-1448.

[4] Yadav D, Singh SP. Mango: History origin and distribution. *J Pharmacogn Phytochem* . 2017;6(6):1257-62.

[5] Coe FG, Anderson GJ. Screening of medicinal plants used by the Garífuna of eastern Nicaragua for bioactive compounds. *J Ethnopharmacol*. 1996;53(1):29-50. doi:10.1016/0378-8741(96)01424-9

[6] Udem GC, Etteh CC, Dahiru D. In vitro antioxidant activities of aqueous and ethanol extracts of *Mangifera indica* leaf, stem-bark and root-bark. *Pharmacognosy Communications*. 2018 Aug;8(3):119-124. DOI: 10.5530/pc.2018.3.25.

[7] Prado Y, Merino N, Acosta J, Herrera J. Acute and 28-day subchronic toxicity studies of mangiferin, a glucosylxanthone isolated from *Mangifera indica* L. stem bark. *J Pharm Pharmacogn Res*. 2015; 3(1):13-23.

[8] Yoshimi N, Matsunaga K, Katayama M, et al. The inhibitory effects of mangiferin, a naturally occurring glucosylxanthone, in bowel carcinogenesis of male F344 rats. *Cancer Lett*. 2001;163(2):163-170. doi:10.1016/s0304-3835(00)00678-9

[9] Laboratory of Laila Nutraceuticals. Personal communication.

[10] Mans RA, Grant A, Pinas N. Plant-Based Ethnopharmacological Remedies for Hypertension in Suriname. In: Builders PF, ed. *Herbal Medicine*. IntechOpen, 2017. DOI: 10.5772/intechopen.72106

[11] Chen Y, Chen Y-p, Liu B-l et al. The Effect of Mangiferin on Improving Endothelial Dysfunction by Inhibiting Endoplasmic Reticulum Stress to Alleviate Mitochondrial Fission. *Am J Clin Exp Med*. 2017;5(5):162-72.

[12] Ronchi SN, Brasil GA, do Nascimento AM, et al. Phytochemical and in vitro and in vivo biological investigation on the antihypertensive activity of mango leaves (*Mangifera indica* L.). *Ther Adv Cardiovasc Dis.* 2015;9(5):244-56. DOI: 10.1177/1753944715572958

[13] Varma Sagi R, Sinha S, Sengupta K. Evaluating inhibition of Reactive Oxygen Species (ROS) generation by herbal products in Phorbol 12-myristate 13-acetate (PMA) induced HL·60 human monocytic cells. Laila Nutra Report No.:LN/CMB/ROS/1515-10-0816_1. 2015. [Data on file]

[14] Varma Sagi R, Sinha S, Sengupta K. To evaluate the modulation of nitrite production in human endothelial cells (EAhy926) by herbal products. Laila Nutra Report No.: LN/CMB/Nitrite/15-12-0870_1. 2015 [Data on file]

[15] Kumar KVN, Sinha S, Sengupta K. Assessment of NADPH Oxidase (NOX) activity inhibition potential of herbal products. Laila Nutra Report No.: LN/CMB/NOX/16-03-0075. 2016 [Data on file]

[16] Kumar KVN, Sinha S, Sengupta K. To estimate the modulation of in L6 Rat skeletal Myoblast cells proliferation by herbal products. Laila Nutra Report No.: LN/CMB/Proliferation/16-03-0063. 2016 [Data on file]

[17] Varma Sagi R, Sinha S, Sengupta K. To estimate the modulation of total cellular protein in L6 Rat skeletal myoblast cells treated with herbal extracts. Laila Nutra Report No.: LN/CMB/Protein/16-03-0062. 2016 [Data on file]

[18] Loya R, Sinha S, Sengupta K. Evaluating the myotube formation capacity of herbal extracts in C2C12 cell line. Laila Nutra Report No.: LN/CMB/Myotube/17-03-0056_1. 2017 [Data on file]

[19] Loya R, Sinha S, Sengupta K. Evaluating the effect of herbal extracts on different muscle markers in rat skeletal muscle cell. Laila Nutra Report No.:LN/CMBIWB/16-03-0090. 2016 [Data on file]

[20] Varma Sagi R, Sinha S, Sengupta K. Evaluating mitochondrial biogenesis activating capacity of herbal extracts in L6 cell line. Laila Nutra Report No. :LN/CMB/Mitogenesis/16-03-0092. 2016 [Data on file]

[21] Gupta S, Sinha S, Sengupta K. Evaluating the effect of herbal extracts on modulation of some key mitochondrial Oxidative Phosphorylation (OX-PHOS) proteins in L6 rat skeletal myoblasts. Laila Nutra Report No.:LN/CMBIWB/16·08·0256_1. 2016 [Data on file]

[22] Zorova LD, Popkov VA, Plotnikov EY, et al. Mitochondrial membrane potential. *Anal Biochem*. 2018 Jul 1;552:50-59.

[23] Geethika N, Kundimi S, Senmgupta K. To evaluate the efficacy of herbal products in stabilizing mitochondrial membrane potential in H_2O_2 induced L-6 rat skeletal myoblasts. Laila Nutra Report No.:LN/CMB/MMP/16-11-0368. 2016 [Data on file]
[24] Tanaka K. The proteasome: overview of structure and functions. *Proc Jpn Acad Ser B Phys Biol Sci*. 2009;85(1):12-36.
[25] Kumar KVN, Sinha S, Sengupta K. Evaluating 20S proteasome inhibiting capacity of herbal extracts in L6 cell line. Laila Nutra Report No.: LN/CMB/20S-UPP/16-1 0-0330. 2016 [Data on file]
[26] Loya R, Kumar A, Kundimi S. Evaluating Testosterone production activating capacity of herbal extracts in MA-1O mouse Leydig cells. Laila Nutra Report No.: LN/CMB/Testosterone/17-08-0195. 2017 [Data on file].
[27] Rao N. Efficacy of LI1254F6 for energy endurance potential in Swiss albino mice. Laila Nutra Study No: L1/PC/16-03-004. 2016 [Data on file]
[28] Rao N. Effect of LI12542F6 supplementation on Dexamethasone induced muscle atrophy in Sprague Dawley rats. Laila Nutra Study No. LI/PC/19-08-015. 2019 [Data on file].
[29] Davis B, Murphy J, Gora O. A Novel Herbal Composition LI12542F6 Improves Muscle Endurance and Strength in Resistance Trained Males (P23-003-19). *Curr Dev Nutr.* 2019;3(Suppl 1). DOI:10.1093/cdn/nzz043.P23-003-19.
[30] [No authors listed] The Effects of a Botanical Blend Supplement (LI12542F6) on Muscle Strength and Endurance During Resistance Training - A Randomized, Double Blind, Placebo Controlled Trial. 2018 [Data on file].
[31] Nestmann ER, Alluri VK, Dodda S, Davis BA. Toxicological studies on the botanical supplement LI12542F6 containing extracts of *Sphaeranthus indicus* flower heads and *Mangifera indica* (mango tree) bark. *Food Sci Nutr*. 2019;7(2):817-833. Published 2019 Jan 29. doi:10.1002/fsn3.931
[32] Generally Recognized as Safe (GRAS) Assessment of the Use of the MyoTOR, a Blend of Sphaeranthus indicus Flower Head Extract and Mangifera indica (Mango Tree) Bark Extract in Foods. March, 2019. [Data on file].