

ExtremeCreatineXXXL+ - Reformulated with Careflow™

Background

Mangifera indica (MI) is an evergreen tree, AKA mango, and yields the mango fruit, one of the most popular tropical fruits. MI fruits contain high levels of beneficial polyphenols (used for over 4,000 years in Ayurvedic and Indigenous medical systems), including Mangiferin, which is commonly used and studied for a multitude of therapeutic applications, including vascular health and anti-inflammatory and neuroprotective effects.¹ For those interested in the use of MI (extracts, food parts, including mangiferin, fruit powder, etc.) in health and disease, please refer to the systematic review by Minniti et al., titled *Mangifera indica* L., *By-Products, and Mangiferin on Cardio-Metabolic and Other Health Conditions: A Systematic Review*.²

The collective findings from the review found mango by-products and derivatives (e.g., leaves, bark, fruit, Mangiferin/extracts, fruit powder, etc.) to directly yield and be associated with many favorable effects. These include enhancements in glycemic control (glucose management) and lipid profiles, including reductions in triglycerides, LDL cholesterol, and total cholesterol, while increasing HDL cholesterol levels. Moreover, mango or extract consumption correlates with reduced appetite and food intake, elevated mood scores, augmented performance during exercise, and decreased incidence of respiratory tract infections.² Custom MI extractions have also been shown to improve endothelial function, including endothelial nitric oxide synthase activation, which leads to increases in nitric oxide (NO) production and subsequent improvements in microcirculation/vasodilation.^{2,3,4,5} This latter benefit is the rationale for the specialized patented MI extract, a fruit powder, trade name Careflow™, to be included in ExtremeCreatineXXXL+ (ECM).^{6,7,8}

Improving Microcirculation (vasodilation and hyperemia)

The role of microcirculation in skeletal muscle is to provide the needed supply of oxygen and various nutrients to support normal muscle protein turnover/health, produce work, and remove waste products of muscle metabolism.⁹ Therefore, enhancing microcirculation through increases in NO production and producing vasodilation and hyperemia (an excess of blood in the vessels) effects may result in a favorable contribution to exercise-induced muscle performance or hypertrophy gains, including helping to amplify the ergogenic and recovery effects of creatine monohydrate and beta-alanine contained in ECM (see [the Practitioner Dietary Supplement Reference Guide NO7RAGE](#) section on vasodilation and hyperemia's potential contributions to performance goals).

MI Fruit Powder Active Ingredient and Unique Preparation (Careflow™)

The primary active ingredient is the polyphenolic compounds derived from MI, particularly mangiferin, flavonoids, phenolic acids, and their derivatives. The preparation used, Careflow™, is a specialized, 100% fruit powder from the MI variety Kili-Mooku, which is harvested at a specific stage when the fruit is green and firm. This precise method is unique because it maintains high levels of bioactive compounds believed to positively affect human physiology, particularly in microcirculation and endothelial function.

Careflow™ Mechanism of Action in Improving Vascular Function

Endothelial-NO synthase (eNOS) is the enzyme that synthesizes nitric oxide (NO), a key molecule responsible for maintaining vascular health by promoting the relaxation and dilation of blood vessels. Activation of eNOS increases NO levels, improving blood flow and endothelial function.¹⁰ NO is a known vasodilator that helps regulate blood flow and mitochondrial respiration,¹¹ including during exercise,^{12,13,14,15} and is thus critical in microcirculation. This means NO is

Practitioner Dietary Supplement Reference Guide – 4th Edition

the most important vasodilator produced by the endothelium (*a monolayer of endothelial cells, making up the inner cellular lining of the blood vessels [arteries, veins, and capillaries] and the lymphatic system, and therefore is in direct contact with the blood/lymph and the circulating cells*) and is generated from L-Arginine (L-Arg) by eNOS.¹⁶ The MI fruit powder, Careflow™, has demonstrated improved microcirculation through its ability to activate eNOS via enhanced activation of both master regulators, [sirtuin-1 \(Sirt 1*\)](#) and [adenosine monophosphate-activated protein kinase \(AMPK**\)](#), which are also critically involved in regulating microcirculation, endothelial function, and overall metabolism.^{6,7,8} Therefore, the fruit powder has a unique influence on three crucial metabolic pathways related to vascular health and performance:

1. AMPK is an energy-sensing enzyme that responds to low energy states by regulating various metabolic processes, including fatty acid oxidation, glucose uptake, and mitochondrial biogenesis.¹⁷ AMPK activation in endothelial cells has been linked to enhanced NO production, as AMPK stimulates the activity of eNOS, leading to increased vasodilation. Studies show Careflow™ stimulates AMPK in endothelial cells, directly enhancing eNOS activity. The increased AMPK activity triggers a cascade that leads to the phosphorylation (activation) of eNOS, thereby increasing NO production.^{6,7,8}
2. Sirt1 is a protein deacetylase that regulates metabolic health and longevity.¹⁸ It modulates energy metabolism, stress response, and mitochondrial function. Sirt1 activation has a direct impact on eNOS by deacetylating and activating it. This promotes NO production, improving endothelial function and vasodilation.¹⁹ Further, Sirt1 enhances mitochondrial efficiency and reduces oxidative stress, indirectly supporting endothelial health and the functionality of eNOS. Careflow™ has been demonstrated to activate Sirt1, suggesting its beneficial effect on eNOS might also be mediated through this pathway.^{6,7,8}
3. Direct effects after digestion. Studies showed that Careflow™, after digestion simulation (which mimics human digestive processes), has a dose-dependent activation effect on eNOS. The bioactive compounds in Careflow™, such as mangiferin, flavonoids, and other phenolic components, are converted during digestion into more active metabolites with a stronger affinity for stimulating eNOS. These metabolites significantly increase the phosphorylation of eNOS, boosting its activity and enhancing NO production.

* Enzymes involved in several biological processes, including cell survival, proliferation, aging, longevity, senescence, apoptosis, DNA repair, and caloric restriction.

** Plays a role in cellular energy homeostasis, mostly to activate glucose and fatty acid uptake and oxidation when cellular energy is low.

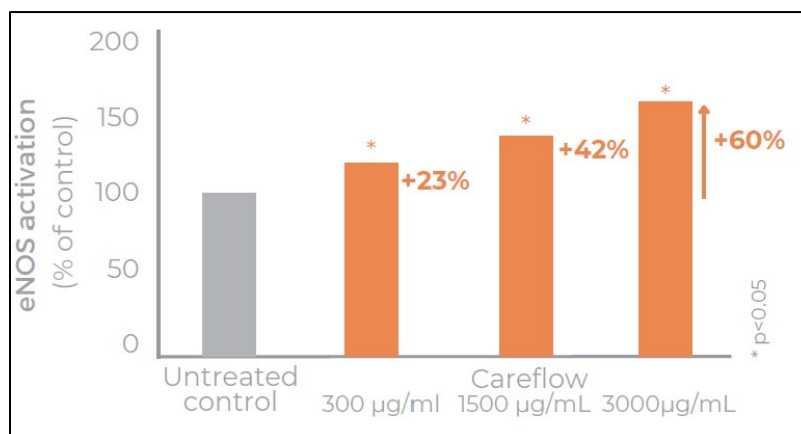


Figure 1 - eNOS Activation at Different Digested Concentrations of Careflow™

Practitioner Dietary Supplement Reference Guide – 4th Edition

Studies Using MI Fruit Powder (Careflow™)

In vitro study on the benefits of a *Mangifera indica* L. fruit powder for well-aging⁸

Rochter et al. performed an in vitro investigation of the MI fruit powder on its effects on master regulators, SIRT1 and AMPK for the aging process. The study found Careflow™ to positively activate these master regulators and other properties related to healthy aging and determined the probable mechanisms of actions as:

1. **Activation of SIRT1 and AMPK** (also described above): The extract activates SIRT1 and AMPK, key regulators of energy homeostasis and cellular metabolism. Activation of these enzymes can mimic the effects of calorie restriction, including activating eNOS and subsequent NO production. This leads to positive vascular health (blood flow), increased fatty acid oxidation, enhanced muscle glucose uptake, and modulation of insulin secretion.
2. **Mitochondrial Biogenesis**: The extract stimulates mitochondrial biogenesis*, which is crucial for maintaining energy production and preventing oxidative stress.
3. **Antioxidative Effects**: The extract augments superoxide dismutase (SOD)** activity, enhancing the body's defense against oxidative stress by breaking down superoxide anions into oxygen and hydrogen peroxide.

* Mitochondrial biogenesis refers to the process by which cells generate new mitochondria, essentially increasing their mitochondrial mass, through the coordinated expression of proteins encoded by both nuclear and mitochondrial DNA, allowing the cell to meet its energy demands by growing and dividing pre-existing mitochondria; this process involves the replication of mitochondrial DNA, synthesis of mitochondrial proteins, and assembly of new mitochondrial structures.

** Superoxide dismutase (SOD) is an enzyme that breaks down harmful oxygen molecules in cells to prevent tissue damage. SOD is found in all living organisms/cells that use oxygen. It's an antioxidant that protects against free radical damage and controls the levels of reactive oxygen species (ROS) and reactive nitrogen species.

Conclusion

Exercisers and others may benefit from this natural preparation/supplement due to its potential to enhance energy metabolism, improve mitochondrial function, and provide antioxidative protection. These effects can lead to better physical performance, increased endurance, and reduced risk of age-related metabolic decline. The activation of SIRT1 and AMPK and subsequent increase in NO production, along with the stimulation of mitochondrial biogenesis, supports overall cellular health and energy homeostasis, making it a valuable supplement for maintaining physical power and muscle mass during aging.⁸

The Gerstgrasser et al. human pilot study was to determine the proper dosage.⁷ Results were that two dosages of Careflow™, 100mg and 300mg, led to an increase in cutaneous blood flow, peaking six hours after ingestion. The increase for the 100mg dosage was statistically significant (54% over baseline), while the increase for the 300mg dosage was not statistically significant (35% over baseline). Therefore, the study indicates that Careflow™ could potentially improve microcirculation and endothelial function, thus supporting its use for improving vascular health, tissue oxygenation, and nutrient delivery, contributing to better overall metabolic health.⁷

Practitioner Dietary Supplement Reference Guide – 4th Edition

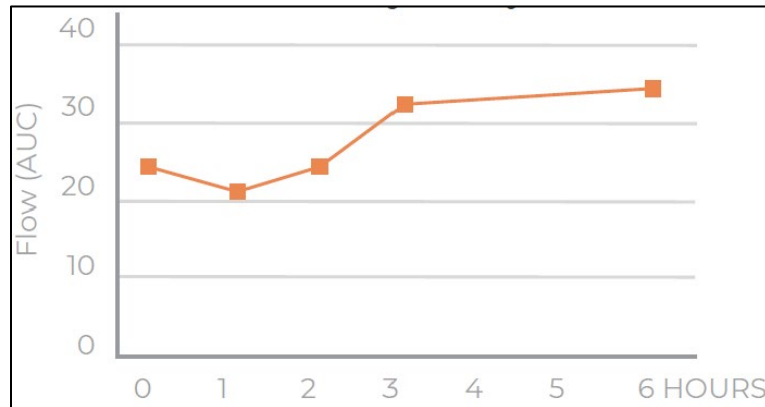


Figure 2 - The blood flow (measured by O2C-system*) was significantly improved with Careflow™ compared to baseline (+54%). Effects almost immediately after ingestion, with maximal effects reached after 6 hours.

(* technique that enables three parameters to be mapped: oxygen saturation (sO₂), relative hemoglobin (rHb), and blood flow.

The Buchwald-Werner et al. follow-up study with Careflow™ included 75 healthy adults to determine its effects on microcirculation and glucose metabolism in a double-blind, randomized placebo controlled 3-arm parallel-design study. Microcirculation improved in the group that received 100mg of the patented fruit powder, especially regarding reactive hyperemia flow. Glucose metabolism was enhanced in the 300mg group, with significant reductions in postprandial glucose levels and a noteworthy decrease in HbA1c values. The study supports that daily supplementation with *Mangifera indica* (Careflow™) can have beneficial effects on microcirculation, endothelial function, and glucose metabolism in healthy individuals. Specifically, A daily dose of 100mg improves microcirculation, particularly increasing the reactive hyperemia flow* (see Figure 3). A higher dose of 300mg enhances glucose metabolism, indicated by reduced postprandial glucose spikes and lower HbA1c levels, which reflect better glucose management over time. Therefore, exercisers (and the population in general) may benefit from experiencing improved microcirculation and subsequent improved nutrient and oxygen delivery to tissues, enhancing exercise performance and recovery. Better glucose management can help maintain energy levels and reduce fatigue during and after workouts. Further, the fruit powder was well-tolerated, with no significant adverse effects, making it a potentially safe addition to daily nutrition for the studied demographic.

*Reactive hyperemia (RH) is a rapid increase in blood flow after a brief period of reduced blood flow. Active hyperemia is high blood flow to meet active muscles' increased need for oxygen.

Practitioner Dietary Supplement Reference Guide – 4th Edition

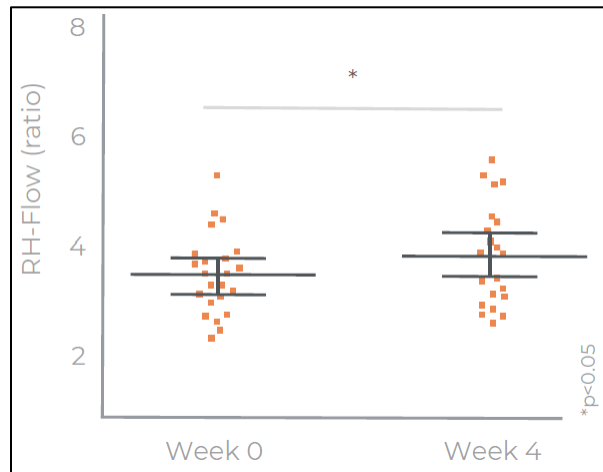


Figure 3 - Reactive hyperemia flow (measured by O2C-System) and the responsiveness of the microvascular system are significantly improved after 4 weeks of supplementation with 100mg of Careflow™.

Ingredient Summary

The patented active ingredient (Careflow™) derived from the MI/mango tree that produces the desired vascular effects, such as hyperemia (increased blood flow) and vasodilation, gets its unique health and NO production powers from its specific harvest stage and 100% fruit powder preparation. Additionally, Careflow™ has been shown to activate two master metabolism and longevity regulators, Sirt1 and AMPK, offering improved energy homeostasis, glucose management, and overall cellular metabolism, including further activating eNOS and subsequent NO production. The desired result is Improved muscle vasodilation and blood volume, leading to greater muscle swelling and metabolism while enhancing the supply of oxygen and various nutrients to support exercise-induced muscle protein turnover/health, work production, and to speed the removal of the waste products of muscle metabolism.

Supplement Facts

Supplement Facts						
Serving Size: 1 Scoop (11g)	Amount Per		Amount Per		Amount Per	
Servings Per Container: 58	1 Scoop	%DV*	2 Scoops	%DV*	3 Scoops	%DV*
Calories	5		10		15	
Total Carbohydrate	1 g	0%	2 g	1%	3g	2%
Calcium	34 mg	3%	68 mg	6%	102 mg	9%
Creatine Monohydrate	2.5 g	*	5 g	*	7.5 g	*
L-Glutamine	3.5 g	*	7 g	*	10.5 g	*
Beta-Alanine	1.6 g	*	3.2 g	*	4.8 g	*
Careflow® Mango Fruit Powder (Mangifera indica L.)	100 mg	*	200 mg	*	300 mg	*

* Daily Value Not Established

Practitioner Dietary Supplement Reference Guide – 4th Edition

References

- ¹ Alaiya, M.A.; Odeniyi, M.A. Utilisation of *Mangifera indica* plant extracts and parts in antimicrobial formulations and as a pharmaceutical excipient: A review. *Future J. Pharm. Sci.* 2023, 9, 29.
- ² Minniti G, Laurindo LF, Machado NM, Duarte LG, Guiguer EL, Araujo AC, Dias JA, Lamas CB, Nunes YC, Bechara MD, Baldi Júnior E, Gimenes FB, Barbalho SM. *Mangifera indica* L., By-Products, and Mangiferin on Cardio-Metabolic and Other Health Conditions: A Systematic Review. *Life (Basel)*. 2023 Nov 28;13(12):2270. doi: 10.3390/life13122270. PMID: 38137871; PMCID: PMC10744517.
- ³ Gelabert-Rebato M, Wiebe JC, Martin-Rincon M, Galvan-Alvarez V, Curtelin D, Perez-Valera M, Habib JJ, Pérez-López A, Vega T, Morales-Alamo D, Calbet JAL. Enhancement of Exercise Performance by 48 Hours, and 15-Day Supplementation with Mangiferin and Luteolin in Men. *Nutrients*. 2019 Feb 6;11(2):344. doi: 10.3390/nu11020344. PMID: 30736383; PMCID: PMC6412949.
- ⁴ Ahmad, R.; Alqathama, A.; Aldholmi, M.; Riaz, M.; Abdalla, A.N.; Aljishi, F.; Althomali, E.; Amir, M.; Abdullah, O.; Alamer, M.A.; et al. Antidiabetic and Anticancer Potentials of *Mangifera indica* L. from Different Geographical Origins. *Pharmaceuticals* 2023, 16, 350
- ⁵ Pinneo, S.; O’Mealy, C.; Rosas, M., Jr.; Tsang, M.; Liu, C.; Kern, M.; Hooshmand, S.; Hong, M.Y. Fresh Mango Consumption Promotes Greater Satiety and Improves Postprandial Glucose and Insulin Responses in Healthy Overweight and Obese Adults. *J. Med. Food* 2022, 25, 381–388
- ⁶ Buchwald-Werner S, Schön C, Frank S, Reule C. Effects of *Mangifera indica* (Careless) on Microcirculation and Glucose Metabolism in Healthy Volunteers. *Planta Med.* 2017 Jul;83(10):824-829. doi: 10.1055/s-0043-103017. Epub 2017 Feb 10. PMID: 28187466.
- ⁷ Gerstgrasser A, Röchter S, Dressler D, Schön C, Reule C, Buchwald-Werner S. In Vitro Activation of eNOS by *Mangifera indica* (Careless™) and Determination of an Effective Dosage in a Randomized, Double-Blind, Human Pilot Study on Microcirculation. *Planta Med.* 2016 Mar;82(4):298-304. doi: 10.1055/s-0035-1558219. Epub 2015 Nov 19. PMID: 26584454.
- ⁸ Röchter, S. & Ehrhardt, Christina & Buchwald-Werner, Sybille & Berger Büter, Karin & Schatton, Elena. (2015). Benefits of a *Mangifera indica* L. fruit powder for well-aging: In vitro investigation of effects on master regulators for the aging process. *Agro Food Industry Hi-Tech*. 26. 4-7.
- ⁹ Hendrickse P, Degens H. The role of microcirculation in muscle function and plasticity. *J Muscle Res Cell Motil.* 2019 Jun;40(2):127-140. doi: 10.1007/s10974-019-09520-2. Epub 2019 Jun 5. PMID: 31165949; PMCID: PMC6726668.
- ¹⁰ Tran N, Garcia T, Aniq M, Ali S, Ally A, Nauli SM. Endothelial Nitric Oxide Synthase (eNOS) and the Cardiovascular System: in Physiology and Disease States. *Am J Biomed Sci Res.* 2022;15(2):153-177. Epub 2022 Jan 4. PMID: 35072089; PMCID: PMC8774925.
- ¹¹ Redaelli S, Magliocca A, Malhotra R, Ristagno G, Citerio G, Bellani G, Berra L, Rezoagli E. Nitric oxide: Clinical applications in critically ill patients. *Nitric Oxide.* 2022 Apr 1;121:20-33. doi: 10.1016/j.niox.2022.01.007. Epub 2022 Feb 2. PMID: 35123061; PMCID: PMC10189363.
- ¹² Barkhidarian, Bahareh et al. “Effects of L-citrulline supplementation on blood pressure: A systematic review and meta-analysis.” *Avicenna Journal of Phytomedicine* vol. 9,1 (2019): 10-20
- ¹³ Jason Cholewa, et al. Effects of dietary sports supplements on metabolite accumulation, vasodilation, and cellular swelling in relation to muscle hypertrophy: A focus on “secondary” physiological determinants. Review article. *Nutrition* 60 (2019) 241–251
- ¹⁴ Bescos, R., Sureda, A., Tur, J. A., & Pons, A. (2012). The effect of nitric-oxide-related supplements on human performance. *Sports Medicine*, 42(2), 99-117
- ¹⁵ Petrovic, V., Buzadzic, B., Korac, A., Vasilijevic, A., Jankovic, A., Micunovic, K., & Korac, B. (2008). Antioxidative defense alterations in skeletal muscle during prolonged acclimation to cold: Role of L-arginine/NO-producing pathway. *The Journal of Experimental Biology*, 211(1), 114-120
- ¹⁶ Tousoulis D., Kampoli A.-M., Papageorgiou N., Stefanadis C. The role of nitric oxide on Endothelial function. *Curr. Vasc. Pharmacol.* 2012;10:4–18. doi: 10.2174/157016112798829760
- ¹⁷ Marín-Aguilar F, Pavillard LE, Giampieri F, Bullón P, Cordero MD. Adenosine Monophosphate (AMP)-Activated Protein Kinase: A New Target for Nutraceutical Compounds. *Int J Mol Sci.* 2017 Jan 29;18(2):288. doi: 10.3390/ijms18020288. PMID: 28146060; PMCID: PMC5343824.
- ¹⁸ Yang Y, Liu Y, Wang Y, Chao Y, Zhang J, Jia Y, Tie J, Hu D. Regulation of SIRT1 and Its Roles in Inflammation. *Front Immunol.* 2022 Mar 11;13:831168. doi: 10.3389/fimmu.2022.831168. PMID: 35359990; PMCID: PMC8962665.
- ¹⁹ Kornberg MD, Sen N, Hara MR, Juluri KR, Nguyen JV, Snowman AM, Law L, Hester LD, Snyder SH. GAPDH mediates nitrosylation of nuclear proteins. *Nat Cell Biol.* 2010 Nov;12(11):1094-100. doi: 10.1038/ncb2114. Epub 2010 Oct 24. PMID: 20972425; PMCID: PMC2972384.