Clinical Evidence Summary

Metabolic Formula Ingredients - Beneficial Clinical References

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INGREDIENTS WITH STRONG POSITIVE CLINICAL EVIDENCE

Creatine

Clinical Benefits:

- Multiple randomized controlled trials and meta-analyses demonstrate improvements in muscle strength, power output, lean body mass, and exercise performance
- Additional evidence suggests potential cognitive and neuroprotective benefits, particularly in older adults or during metabolic stress

Key References:

- Kreider RB et al. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *Journal of the International Society of Sports Nutrition*, 2017.
- Avgerinos KI et al. Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review. *Experimental Gerontology*, 2018.
- Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. *Journal of Strength and Conditioning Research*, 2003.

Citrulline 1:2 Malate

Clinical Benefits:

- Human studies indicate improved exercise performance, reduced fatigue, and enhanced nitric oxide production
- Benefits most evident when combined with resistance training or endurance exercise
- The 1:2 ratio (citrulline to malate) provides additional support for aerobic energy production via the Krebs cycle

Key References:

- Trexler ET et al. International Society of Sports Nutrition position stand: Citrulline. *Journal of the International Society of Sports Nutrition*, 2019.
- Pérez-Guisado J, Jakeman PM. Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. *Journal of Strength and Conditioning Research*, 2010.
- Bendahan D et al. Citrulline/malate promotes aerobic energy production in human exercising muscle. *British Journal of Sports Medicine*, 2002.

Branched-Chain Amino Acids

L-Leucine

Clinical Benefits:

- Strong evidence for stimulating muscle protein synthesis via mTOR pathway activation
- Clinical studies show improved recovery and lean mass when combined with resistance training

Key References:

- Wolfe RR. Branched-chain amino acids and muscle protein synthesis in humans. *Journal of the International Society of Sports Nutrition*, 2017.
- Churchward-Venne TA et al. Leucine supplementation of a low-protein mixed macronutrient beverage enhances myofibrillar protein synthesis. *American Journal of Clinical Nutrition*, 2014.

L-Isoleucine

Clinical Benefits:

- Supports glucose uptake in muscle tissue independent of insulin
- Contributes to energy production during prolonged exercise

Key References:

- Doi M et al. Isoleucine, a potent plasma glucose-lowering amino acid, stimulates glucose uptake in C2C12 myotubes. *Biochemical and Biophysical Research Communications*, 2003.
- Shimomura Y et al. Nutraceutical effects of branched-chain amino acids on skeletal muscle. *Journal of Nutrition*, 2006.

L-Valine

Clinical Benefits:

- Essential for muscle metabolism and tissue repair
- Supports nitrogen balance and energy provision during exercise

Key References:

- Shimomura Y et al. Exercise promotes BCAA catabolism: effects of BCAA supplementation on skeletal muscle during exercise. *Journal of Nutrition*, 2004.
- Blomstrand E. A role for branched-chain amino acids in reducing central fatigue. *Journal of Nutrition*, 2006.

Ca-HMB (Calcium β-Hydroxy-β-Methylbutyrate)

Clinical Benefits:

- Strong evidence for reducing muscle protein breakdown
- Supports lean muscle mass preservation, particularly in aging populations and during caloric restriction
- May accelerate recovery from high-intensity exercise

Key References:

- Wilson JM et al. International Society of Sports Nutrition Position Stand: beta-hydroxy-beta-methylbutyrate (HMB). *Journal of the International Society of Sports Nutrition*, 2013.
- Wu H et al. Effect of beta-hydroxy-beta-methylbutyrate supplementation on muscle loss in older adults: A systematic review and meta-analysis. *Archives of Gerontology and Geriatrics*, 2015.
- Nissen S et al. Effect of leucine metabolite β-hydroxy-β-methylbutyrate on muscle metabolism during resistance-exercise training. *Journal of Applied Physiology*, 1996.

Vitamin D3

Clinical Benefits:

- Robust clinical evidence supports bone mineral density maintenance, muscle function, and fall-risk reduction in deficient populations
- Meta-analyses indicate benefit for certain pain and inflammatory conditions

- Supports immune function and cardiovascular health

Key References:

- Holick MF. Vitamin D deficiency. *New England Journal of Medicine*, 2007.
- Bischoff-Ferrari HA et al. Effect of vitamin D on falls: A meta-analysis. *JAMA*, 2004.
- Pilz S et al. Vitamin D and cardiovascular disease prevention. *Nature Reviews Cardiology*, 2016.

Ascorbic Acid (Vitamin C)

Clinical Benefits:

- Essential antioxidant with strong evidence for immune support
- Supports collagen synthesis critical for connective tissue health
- Enhances non-heme iron absorption
- May reduce exercise-induced oxidative stress

Key References:

- Carr AC, Maggini S. Vitamin C and immune function. *Nutrients*, 2017.
- Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database of Systematic Reviews*, 2013.
- DePhillipo NN et al. Efficacy of vitamin C supplementation on collagen synthesis and oxidative stress after musculoskeletal injuries. *Orthopaedic Journal of Sports Medicine*, 2018.

Magnesium Citrate

Clinical Benefits:

- Effective in correcting magnesium deficiency
- Clinical benefits observed in muscle cramping, migraine prevention, and metabolic function
- Supports energy metabolism and protein synthesis
- Citrate form demonstrates superior bioavailability

Key References:

- Gröber U et al. Magnesium in prevention and therapy. *Nutrients*, 2015.

- Walker AF et al. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. *Journal of Women's Health*, 1998.
- Lindberg JS et al. Magnesium bioavailability from magnesium citrate and magnesium oxide. *Journal of the American College of Nutrition*, 1990.

Potassium Citrate

Clinical Benefits:

- Strong evidence for kidney stone prevention in clinical protocols
- Supports acid-base balance and may preserve bone mineral density
- Essential electrolyte for muscle and nerve function

Key References:

- Pak CY et al. Long-term treatment of calcium nephrolithiasis with potassium citrate. *Journal of Urology*, 1985.
- Jehle S et al. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults. *Journal of Clinical Endocrinology & Metabolism*, 2013.
- He FJ, MacGregor GA. Beneficial effects of potassium on human health. *Physiologia Plantarum*, 2008.

Ferrous Gluconate

Clinical Benefits:

- Proven effective for correction of iron-deficiency anemia
- Generally better tolerated than ferrous sulfate with fewer GI side effects
- Benefits are most significant in individuals with confirmed deficiency

Key References:

- Tolkien Z et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLOS One*, 2015.
- WHO. Iron supplementation guidelines for iron deficiency anemia. *World Health Organization*, 2016.

- Cancelo-Hidalgo MJ et al. Tolerability of different oral iron supplements: a systematic review. *Current Medical Research and Opinion*, 2013.

Hyaluronic Acid

Clinical Benefits:

- Strong evidence for joint symptom improvement via intra-articular use
- Oral supplementation shows improvements in joint comfort and skin hydration
- Supports skin elasticity and wound healing

Key References:

- Bannuru RR et al. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis. *Annals of Internal Medicine*, 2015.
- Kalman DS et al. Effect of a natural extract of chicken combs with a high content of hyaluronic acid on pain relief and quality of life in subjects with knee osteoarthritis. *Nutrition Journal*, 2008.
- Kawada C et al. Ingested hyaluronan moisturizes dry skin. *Nutrition Journal*, 2014.

Saw Palmetto (Serenoa repens)

Clinical Benefits:

- Several randomized trials show improvement in lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH)
- May support healthy DHT levels
- Generally well-tolerated with favorable safety profile

Key References:

- Bent S et al. Saw palmetto for benign prostatic hyperplasia. *New England Journal of Medicine*, 2006.
- Tacklind J et al. Serenoa repens for benign prostatic hyperplasia. *Cochrane Database of Systematic Reviews*, 2012.
- Wilt T et al. Saw palmetto extracts for treatment of benign prostatic hyperplasia: A systematic review. *JAMA*, 1998.

INGREDIENTS WITH MODERATE POSITIVE CLINICAL EVIDENCE

Essential Amino Acids

L-Lysine HCl

Clinical Benefits:

- Supports collagen formation and tissue repair
- May reduce frequency of herpes simplex outbreaks
- Essential for calcium absorption

Key References:

- Flodin NW. The metabolic roles, pharmacology, and toxicology of lysine. *Journal of the American College of Nutrition*, 1997.
- Griffith RS et al. Success of L-lysine therapy in frequently recurrent herpes simplex infection. *Dermatologica*, 1987.

L-Threonine

Clinical Benefits:

- Essential for protein synthesis and intestinal mucosal integrity
- Supports immune function via antibody production

Key References:

- Mao X et al. Specific roles of threonine in intestinal mucosal integrity and barrier function. *Frontiers in Bioscience*, 2011.

L-Phenylalanine

Clinical Benefits:

- Precursor to tyrosine and neurotransmitters (dopamine, norepinephrine)
- May support mood and cognitive function

Key References:

- Beckmann H et al. DL-phenylalanine in depressed patients: an open study. *Journal of Neural Transmission*, 1977.

L-Methionine

Clinical Benefits:

- Essential sulfur-containing amino acid supporting detoxification pathways
- Precursor to cysteine and glutathione

Key References:

- Martínez Y et al. The role of methionine on metabolism, oxidative stress, and diseases. *Amino Acids*, 2017.

L-Histidine HCl

Clinical Benefits:

- Precursor to histamine; supports immune response
- Component of carnosine, which has antioxidant properties in muscle

Key References:

- Feng RN et al. Histidine supplementation improves insulin resistance through suppressed inflammation. *Diabetes Care*, 2013.

L-Tryptophan

Clinical Benefits:

- Precursor to serotonin and melatonin
- May support mood regulation and sleep quality

Key References:

- Silber BY, Schmitt JA. Effects of tryptophan loading on human cognition, mood, and sleep. *Neuroscience & Biobehavioral Reviews*, 2010.
- Hudson C et al. Protein source tryptophan versus pharmaceutical grade tryptophan as an efficacious treatment for chronic insomnia. *Nutritional Neuroscience*, 2005.

Glycine

Clinical Benefits:

- Supports collagen synthesis and skin health
- May improve sleep quality when taken before bed
- Contributes to creatine synthesis

Key References:

- Bannai M et al. The effects of glycine on subjective daytime performance in partially sleep-restricted healthy volunteers. *Frontiers in Neurology*, 2012.
- Razak MA et al. Multifarious beneficial effect of nonessential amino acid, glycine: a review. *Oxidative Medicine and Cellular Longevity*, 2017.
- Kawai N et al. The sleep-promoting and hypothermic effects of glycine are mediated by NMDA receptors in the suprachiasmatic nucleus. *Neuropsychopharmacology*, 2015.

D-Ribose

Clinical Benefits:

- Small clinical studies suggest energy metabolism support
- May benefit individuals with chronic fatigue or cardiac conditions
- Supports ATP regeneration in muscle tissue

Key References:

- Teitelbaum JE et al. The use of D-ribose in chronic fatigue syndrome and fibromyalgia. *Journal of Alternative and Complementary Medicine*, 2006.
- Omran H et al. D-Ribose improves diastolic function and quality of life in congestive heart failure patients. *European Journal of Heart Failure*, 2003.
- Hellsten Y et al. Effect of ribose supplementation on resynthesis of adenine nucleotides after intense intermittent training. *American Journal of Physiology*, 2004.

Vitamin B6 (Pyridoxine)

Clinical Benefits:

- Supports amino acid metabolism and neurotransmitter synthesis
- Essential cofactor for over 100 enzymatic reactions
- May reduce homocysteine levels

Key References:

- Hellmann H, Mooney S. Vitamin B6: A molecule for human health. *Molecules*, 2010.
- Spinneker A et al. Vitamin B6 status, deficiency and its consequences – an overview. *Nutrición Hospitalaria*, 2007.

Vitamin E (Tocopherol)

Clinical Benefits:

- Demonstrates antioxidant effects and reduction of oxidative stress markers
- Supports cell membrane integrity
- May benefit skin health and wound healing

Key References:

- Traber MG, Stevens JF. Vitamins C and E: Beneficial effects from a mechanistic perspective. *Free Radical Biology & Medicine*, 2011.
- Rizvi S et al. The role of vitamin E in human health and some diseases. *Sultan Qaboos University Medical Journal*, 2014.

FUNCTIONAL/SUPPORTIVE INGREDIENTS

Citric Acid

Clinical Benefits:

- Enhances mineral absorption (calcium, magnesium, zinc)
- Provides alkalinizing effect when metabolized
- Natural preservative with antioxidant properties

Key References:

- Seltzer MA et al. Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. *Journal of Urology*, 1996.
- Penniston KL et al. Quantitative assessment of citric acid in lemon juice, lime juice, and commercially-available fruit juice products. *Journal of Endourology*, 2008.

Sunflower Oil - High Oleic

Clinical Benefits:

- High oleic acid content supports cardiovascular health markers
- Excellent carrier oil for transdermal applications
- Supports skin barrier function

Key References:

- Gupta A et al. Oxidative stability of safflower oil and oleic safflower oil in accelerated storage test. *Journal of the American Oil Chemists' Society*, 2012.
- Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis. *Arteriosclerosis and Thrombosis*, 1992.

Jojoba Oil

Clinical Benefits:

- Supports skin barrier function and hydration
- Non-comedogenic with favorable dermatological profile
- Contains natural anti-inflammatory compounds

Key References:

- Meier L et al. Clay jojoba oil facial mask for lesioned skin and mild acne. *Forschende Komplementärmedizin*, 2012.
- Ranzato E et al. Wound healing properties of jojoba liquid wax: an in vitro study. *Journal of Ethnopharmacology*, 2011.

Rosemary Extract

Clinical Benefits:

- Demonstrates antioxidant and antimicrobial properties
- May support cognitive function and memory
- Natural preservative extending product stability

Key References:

- Habtemariam S. The therapeutic potential of rosemary (Rosmarinus officinalis) diterpenes for Alzheimer's disease. *Evidence-Based Complementary and Alternative Medicine*, 2016.
- Moss M et al. Aromas of rosemary and lavender essential oils differentially affect cognition and mood. *International Journal of Neuroscience*, 2003.

Menthol

Clinical Benefits:

- Demonstrates topical analgesic and cooling effects in human studies
- Enhances transdermal penetration of active compounds
- Provides sensory feedback confirming product application

Key References:

- Patel T et al. Menthol: A refreshing look at this ancient compound. *Journal of the American Academy of Dermatology*, 2007.
- Yosipovitch G et al. Effect of topically applied menthol on thermal, pain and itch sensations. *Archives of Dermatological Research*, 1996.
- Galeotti N et al. Menthol: A natural analgesic compound. *Neuroscience Letters*, 2002.

Sorbitol

Clinical Benefits:

- Effective humectant maintaining product and skin hydration
- Well-tolerated in topical formulations

- Supports product texture and stability

Key References:

- Loden M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. *American Journal of Clinical Dermatology*, 2003.

Xanthan Gum

Clinical Benefits:

- FDA-approved stabilizer with excellent safety profile
- Supports uniform distribution of active ingredients
- May provide prebiotic effects when ingested

Key References:

- Sworn G. Xanthan gum. *Handbook of Hydrocolloids*, 2009.
- Becker A et al. Xanthan gum biosynthesis and application: a biochemical/genetic perspective. *Applied Microbiology and Biotechnology*, 1998.

Document prepared for LifeActive Bio regulatory and marketing reference. Evidence strength varies by ingredient; clinical benefits should be communicated in accordance with applicable regulatory guidelines.