This document contains partial reference to clinical studies for some of the ingredient utilized in Lean Optimizer™. For additional references, including hard-copy files, please send requests to:

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**Advanta-Z**

**Efficacy**

Jan 2012  
**The naturally occurring p-synephrine in Advantra Z will exhibit at least twice the physiological activity compared to an equal weight of synthetic p-synephrine.**  
Stereochemical and Physiological Differences between Naturally Occurring p-Synephrine and Synthetic p-Synephrine - Stohs and Preuss, *Journal of Functional Foods*

Mar 2011  
**Ingestion of a multi-ingredient weight management supplement containing Advantra Z, caffeine and green tea extract increased resting metabolic rate, but did not lead to increased cardiovascular stress.**  
Effect of Acute Administration of an Herbal Preparation on Blood Pressure and Heart Rate in Humans - Seifert, *International Journal of Medical Sciences* †

Mar 2008  
**Exercise was easier 83% of the time - and no significant adverse events occurred - following use of a performance-enhancing dietary supplement containing Advantra Z.**  
Human Pharmacology of a Performance-Enhancing Dietary Supplement Under Resting and Exercise Conditions - Haller, University of California, San Francisco, *British Journal of Clinical Pharmacology* †

May 2006  
**Consuming an enriched coffee beverage containing bitter orange (e.g. Advantra Z) increased resting energy expenditures. No differences in average heart rate and blood pressure were observed.**  

2006  
**A multi-ingredient supplement containing Advantra Z increased energy production and fat oxidation.**  
Metabolic and Physiological Effects of Ingesting Extracts of Bitter Orange, Green Tea and Guarana at Rest and During Treadmill Walking in Overweight Males - Sale,
A three-part study conducted over a period of six years supports the efficacy of Advantra Z - Gougeon, McGill University, Obesity Research

- **Increase in the Thermic Effect of Food by Adrenergic Amines Extracted from Citrus aurantium**
  Increase in the Thermic Effect of Food by Adrenergic Amines Extracted from Citrus aurantium - Gougeon

- **Advantra Z caused a measurable increase in the metabolic rate in obese subjects.**
  Thermic Effect of Citrus aurantium in Obese Subjects - Pathak

- **Advantra Z increased the thermic effect of food in lean subjects after consumption of a meal, resulting in a measurable increase in metabolic rate without heart rate or blood pressure irregularities.**
  Thermic Effect of Beta-Sympathicomimetic Compounds Extracted from Citrus aurantium in Humans - Hedrei

**2005**

A multi-ingredient supplement containing Advantra Z was more effective in inducing weight loss than diet and exercise alone.
Effect of a Multi-Ingredient Weight-Loss Product on Body Composition in Overweight Adult Men and Women - Zenk †

**May 2004**

A multi-ingredient supplement containing Advantra Z reversed the decrease in resting metabolic rate associated with calorie restriction in overweight adults without serious adverse events.
Effect of Multi-Ingredient Weight-Loss Product on Metabolic Rate and Body Composition - Zenk, Journal Nutrition †

**2003**

A multi-ingredient supplement containing Advantra Z significantly enhanced metabolism without negatively affecting blood pressure.
Efficacy of a Commercial Green Tea Extract/Caffeine-Based Product to Increase Basal Metabolism in Healthy Adults - Kalman

**2003**

A multi-ingredient product containing Advantra Z reduced fatigue and curbed appetite in overweight adults without serious adverse events.
An Acute Clinical Trial to Evaluate the Safety and Efficacy of a Popular Weight Loss Supplement When Used with Exercise - Kalman †

**2002**

Citrus aurantium (e.g., Advantra Z) may be the best thermogenic substitute for ephedra.
Citrus aurantium as a Thermogenic, Weight Reduction Replacement for Ephedra: An Overview - Preuss, Journal of Medicine

**Sep 2000**

A multi-ingredient supplement containing Advantra Z aided weight loss - particularly during the first, frustrating weeks of dieting - without causing serious adverse events.
Study on the Effectiveness of a Multi-Ingredient Supplement for the Reduction of Body Weight - Kendall-Reed

Mar 1999 A multi-ingredient supplement containing Advantra Z was effective in promoting weight and fat loss - without significant changes in blood pressure and heart rate - when combined with diet and exercise. Effects of Citrus aurantium Extract, Caffeine and St. John's Wort on Body Fat Loss, Lipid Levels, and Mood States in Overweight Healthy Adults - Colker, Current Therapeutic Research

Mechanism of Action

Jun 2011 p-Synephrine - the dominant amine in Advantra Z - binds to beta-3 adrenergic receptors that trigger lipolysis. p-Synephrine exhibits little or no binding to alpha-, beta-1 and beta-2 adrenergic receptors, which are associated with increases in heart rate and blood pressure. A Review of the Receptor-Binding Properties of p-Synephrine as Related to Its Pharmacological Effects - Stohs, Oxidative Medicine and Cellular Longevity

Apr 2007 Synephrine-rich orange peel induced lipolysis in fat cells. Lipolysis Induced by Segment Wall Extract from Satsuma Mandarin Orange - Tsujita, Ehime University, Journal of Nutritional Science and Vitaminology

Aug 2003 The alkaloids in Advantra Z are biologically and physiologically distinct from those found in ephedra, due to differences in pharmacokinetics and pharmacodynamics. The most obvious difference is that Advantra Z, unlike ephedra, does not readily pass into the brain. The Difference between Citrus aurantium Extract (Advantra Z) and Ephedra Extract - Jones

Jun 2002 Advantra Z primarily stimulates beta 3 receptors, which are responsible for triggering thermogenesis. It does not cross the blood/brain barrier, making minimal contact with the excitatory receptors that cause negative cardiovascular and central nervous systems side effects. Advantra Z: Observation on its Effects and Mechanism of Action - Jones


Safety/Toxicity

April 2013 A single one-time dose, up to 70 mg p-synephrine alone or 40 mg in combination with 320 mg of caffeine is not likely to cause adverse effects. If taken as divided doses spaced out over the course of a day, 100 mg of p-synephrine alone (e.g., 50 mg twice a day or 33 mg three times daily) or 70 mg in combination with 400 mg of caffeine is unlikely to be associated with adverse effects. Review of the Safety Data Available on p-Synephrine, Caffeine, and p-Synephrine-Caffeine Containing Combination Products. - Intertek Cantox
May 2011 | 1 to 50 mg of p-synephrine, the dominant amine in Advantra Z, per day for healthy adults is not likely to cause adverse health consequences - nor are products providing up to 40 mg of p synephrine in combination with a maximum of 320 mg of caffeine per day.

Synephrine, Octopamine and Caffeine Health Risk Assessment Report, Marles, Health Canada Natural Health Products Directorate, File No. 172091

May 2011 | High dosages of bitter orange (e.g., Advantra Z) and its primary amine, p synephrine, did not produce maternal or fetal toxicity in rats - even when combined with caffeine.

Developmental Toxicity of Citrus aurantium in Rats - Hansen, Birth Defects Research Part B: Developmental and Reproductive Toxicology

Apr 2011 | An analysis of the chemistry and safety of bitter orange (e.g., Advantra Z) drawn from more than 50 research studies and reference sources concluded that bitter orange - alone or in combination with caffeine and other ingredients - has no effect on blood pressure or heart rate.

The Safety of Citrus aurantium (Bitter Orange) and its Primary Protoalkaloid p-Synephrine - Stohs and Preuss, Phytotherapy Research

Feb 2011 | Based on current research and the extensive ingestion of products containing bitter orange (e.g., Advantra Z), bitter orange extract is safe for human consumption, and challenges to the safety of this ingredient are without scientific basis.

The Safety of Bitter Orange (Citrus aurantium) and p-Synephrine - Stohs and Preuss, HerbalGram

Nov 2010 | Bitter orange, the source of Advantra Z, was not linked to adverse events presented in the 22 reports received between April 2004 and October 2009.

Assessment of the Adverse Event Reports (AERS) Associated with Citrus aurantium (bitter orange) from April 2004 to October 2009, Stohs, Journal of Functional Foods

Oct 2010 | Advantra Z contains only p-synephrine, a stable isomer of the synephrine alkaloid; it does not contain m-synephrine, which has the potential for raising blood pressure.

Sani-Pure Food Laboratories

2009 | Researchers observed a reduction in body weight gain, but no effects on organ weights or biochemical/hematological parameters when low to high doses of bitter orange (e.g., Advantra Z) and p-synephrine were administered to mice.

Subchronic Toxicity of Citrus aurantium L. (Rutaceae) Extract and p-Synephrine in Mice - Arbo, Regulatory Toxicology and Pharmacology


Citrus aurantium Extract has No Effect on Blood Pressure or Heart Rate in Healthy Adults - Talbott, Experimental Biology
April 2006  
**A single-dose bitter orange (e.g., Advantra Z) did not cause a false-positive response to the CEDIAs amphetamines assay.**
Response of CEDIAs Amphetamines Assay after a Single Dose of Bitter Orange - Nguyen, University of California, San Francisco, *Therapeutic Drug Monitoring*

November 2005  
**Advantra Z had virtually no impact on blood pressure or heart rate.**
Absence of QTc Interval-Prolonging or Hemodynamic Effects of a Single Dose of Bitter-Orange Extract in Healthy Subjects - Min, University of Connecticut, *Pharmacotherapy* †

September 2005  
**Advantra Z had little or no effect on the central nervous system and did not cause any increase in blood pressure in doses relevant to dietary supplements on the market.**
Hemodynamic Effects of Ephedra Free Weight Loss Supplements in Humans - Haller, University of California, San Francisco, *American Journal of Medicine* †

September 2004  
**Analysis of 147 adverse event reports could not establish bitter orange as the cause of the adverse events.**

June 2004  
**Bitter orange (e.g., Advantra Z) does not have ephedra's negative cardiovascular and central nervous system side effects.**
National Toxicology Study on Bitter Orange - National Institute of Health

2004  
**Long-term, daily administration of bitter orange extract (e.g., Advantra Z) does not cause negative herb drug interactions.**
Pharmokenetics and Drug Disposition - Gurley, *American Society of Clinical Pharmacology and Therapeutics*

2001  
**Cardiovascular indices were not significantly altered by Seville orange juice ingestion, even though the juice contained marked amounts of synephrine.**
Seville (sour) Orange Juice: Synephrine Content and Cardiovascular Effects in Normotensive Adults - Penzak, *Journal of Clinical Pharmacology*

July 1997  
**The acute oral LD50 toxicity test of Advantra Z was greater than 10,000 mg per kilogram.**
An Acute Oral Toxicity Study in Rats with Advantra Z - Douds
Hoodia Gordonii

- Avula B, Wang YH, Pawar RS, Shukla YJ, Smillie TJ, Khan IA. A rapid method for chemical fingerprint analysis of Hoodia species, related genera, and dietary supplements using UPLC-UV-MS. J Pharm Biomed Anal 2008; 48: 722-31. PubMed Citation (The demand for Hoodia gordonii has resulted in use of other species which may not have appetite suppressant activity; using chromatography and mass spectrometry, it is possible to identify the fingerprint of the 12 hoodigosides and correctly identify products from H. gordonii).
- van Heerden FR. Hoodia gordonii: a natural appetite suppressant. J Ethnopharmacol 2008; 119: 434-7. PubMed Citation (Hoodia is a multistemmed succulent which is classified as a stapeliad [and not related to the cactus family], which is found in South Africa and was used by native people as food and to quench thirst, but has been marketed and become popular as an appetite suppressant, the clinical bases for the claims being weak; hoodia contains multiple pregnane glycosides which are being evaluated for appetite suppressant activity).
- Whelan AM, Jurgens TM, Szeto V. Case report. Efficacy of Hoodia for weight loss: is there evidence to support the efficacy claims? J Clin Pharm Ther 2010; 35: 609-12 PubMed Citation (Review of literature on hoodia found no prospective control trials of its efficacy; open label studies reported that its appetite suppressing activity was promising and that it had no adverse events).
- Blom WA, Abrahamse SL, Bradford R, Duchateau GS, Theis W, Orsi A, Ward CL, Mela DJ. Effects of 15-d repeated consumption of Hoodia gordonii purified extract on safety, ad libitum energy intake, and body weight in healthy, overweight women: a randomized controlled trial. Am J Clin Nutr 2011; 94: 1171-81. PubMed Citation (In a controlled trial of 15 days of hoodia vs placebo in 49 overweight women, hoodia was associated with abnormal skin sensitivity, nausea, vomiting, increases in blood pressure and elevations in total [indirect] bilirubin and Alk P without a change in ALT levels, clinically apparent liver injury or decrease in caloric intake).
5-HTP

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7-Keto


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**Guggulsterones**

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- Burris TP, et al. The Hypolipidemic Natural Product Guggulsterone is a Promiscuous Steroid Receptor Ligand. Mol Pharmacol. 67(3): 948-954. 2005
- Panda S, Kar A. Guggulu (Commiphora mukul) potentially ameliorates hypothyroidism in female mice. Phytother Res. 19(1):78-80. 2005. Thyroid Research Unit, School of Life Sciences, D. A. University, Indore, India.
- Szapary PO, et al, Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trialJAMA. 13;290(6):765-72. 2003. Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104-6021, USA.
Chromium

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Alpha Lipoic Acid

- α-lipoic acid can improve endothelial dysfunction in subjects with impaired fasting glucose
- Lipoic Acid Biosynthesis: LipA Is an Iron–Sulfur Protein
- Reed LJ. From lipoic acid to multi-enzyme complexes. Protein Sci. (1998)
- The Chemistry of 1,2-Dithiolane (Trimethylene Disulfide) As a Model for the Primary Quantum Conversion Act in Photosynthesis
- Interrelationships of Lipoic Acids
- Preparation and use of salts of the pure enantiomers of alpha-lipoic acid
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• Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress


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• Seo EY, Ha AW, Kim WK. α-Lipoic acid reduced weight gain and improved the lipid profile in rats fed with high fat diet. *Nutr Res Pract.* (2012)


• Butler JA, Hagen TM, Moreau R. Lipoic acid improves hypertriglyceridemia by stimulating triacylglycerol clearance and downregulating liver triacylglycerol secretion. *Arch Biochem Biophys.* (2009)


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Ferreira PM, Militão GC, Freitas RM. Lipoic acid effects on lipid peroxidation level, superoxide dismutase activity and monoamines concentration in rat hippocampus. *Neurosci Lett.* (2009)


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Antioxidants preserve redox balance and inhibit c-Jun-N-terminal kinase pathway while improving insulin signaling in fat-fed rats: evidence for the role of oxidative stress on IRS-1 serine phosphorylation and insulin resistance.


Chou TC, Shih CY, Chen YT. Inhibitory effect of α-lipoic acid on platelet aggregation is mediated by PPARs. *J Agric Food Chem.* (2011)
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