

## Clinical Stress Relief

### TECHNICAL SUMMARY

Clinical Stress Relief features Lactium®, a clinically tested milk protein derivative. Lactium® has been shown to support healthy cortisol levels and thus, can help to relieve the symptoms of stress from everyday life.\* In addition, it can help to bring on sleep more quickly, maintain uninterrupted sleep, and promote better overall sleep quality.\* Ashwagandha has been included as an “adaptogen,” which helps the body adapt to typical daily stress.\*

#### Structure formula:

Lactium®:  $\alpha_{S1}$ -casein (f91-100) or  $\alpha$ -casozepine is a unique decapeptide obtained from the tryptic hydrolysis of  $\alpha_{S1}$ -casein from bovine milk. It is made of residues f91-100 from  $\alpha_{S1}$ -casein (sequence: YLGYLEQLLR, 1266.6 Da).

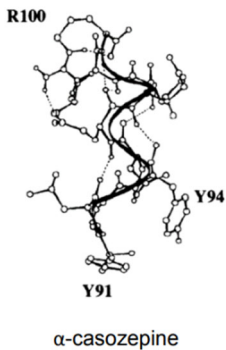


Figure 1: Lactium®

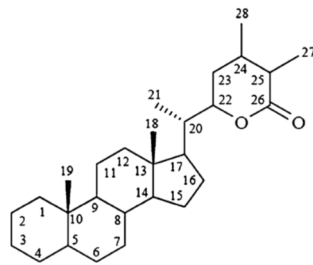


Figure 2: Withanolide skeleton.

Ashwagandha extract: Among the more than 35 chemical constituents isolated from ashwagandha root, withanolides, a group of steroidal lactones, are believed to be the main bioactive compounds. The basic skeleton of withanolides is 22-hydroxyergostan-26-oic acid-26,22-lactone. Withaferin A (4 $\beta$ , 27-dihydroxyl-1-oxo-5 $\beta$ , 6 $\beta$ -epoxywitha-2-24-dienolide) was the first member of this group of compounds to be isolated.

**Allergen and Additive Disclosure:** Not manufactured with yeast, wheat, gluten, soy, egg, fish, shellfish, tree nut or sesame ingredients. Produced in a GMP facility that processes other ingredients containing these allergens.

**Delivery Form:** Vegetable Capsule

### ROLE AS NUTRIENT/FUNCTION

Lactium®: Laboratory studies indicate that Lactium® derived from milk has a high affinity for the benzodiazepine side of GABA<sub>A</sub> receptor.\*

Ashwagandha: Because of the complex makeup of bioactive compounds found in ashwagandha roots, their physiological functions have not been completely elucidated at this time. Withanolides have been extensively studied and laboratory data suggest that they are involved in some of the following functional properties of ashwagandha:

- CNS: Data from laboratory experiments suggest that ashwagandha interacts with the GABA<sub>A</sub> receptor system as well as many other neurologic pathways.\*
- Immune support: Withanolides are known to interfere with the nuclear factor kappa B system, which may partially explain the effects of

## Supplement Facts

Serving Size 1 Veg Capsule

### Amount Per Serving

Casein Hydrolysate (Bioactive Milk Peptides) (Lactium®)	150 mg**
Ashwagandha Extract ( <i>Withania somnifera</i> ) (Root and Leaf) (min. 2.5% Total Withanolides)	300 mg**

\*\* Daily Value not established.

Other ingredients: Hypromellose (cellulose capsule), Stearic Acid (vegetable source) and Silicon Dioxide.

- Mood & Sleep Support\*
- Support for Everyday Stress\*

**SUGGESTED USAGE:** Take 1 capsule 1 to 2 times daily, with or without food, or as directed by your healthcare practitioner. May be taken during daytime for stress or before bed to help with sleep.\*

ashwagandha on the immune system.\* Other data suggest that withanolides are involved in the regulation of the immune response, favoring a specific pathway that increases macrophage functions.\*

Oxidative damage: In studies on model animals, ashwagandha was able to limit lipid peroxidation and superoxide dismutase activities and enhance the activities of catalase and glutathione peroxidase.\*

### NATUROKINETICS®

**Liberation:** Vegetable capsules disintegrate within 60 minutes in a USP water disintegration test.

The absorption, distribution, metabolism and elimination of Lactium® have not been studied in humans. The structural nature of Lactium® suggests it would be handled by the body like other dietary peptides. Data from laboratory experiments show it possesses a certain resistance toward gastric and pancreatic proteases, as well as increased transport across intestinal cells in the presence of bile salts, suggesting that Lactium® may reach the bloodstream intact after ingestion.

Absorption, distribution, metabolism and elimination of ashwagandha have not been studied in humans; however, data from model animals helps us to extrapolate the Naturokinetics® of ashwagandha.

**Absorption:** Data from animal models suggest a rapid absorption of withanolides. In a study performed on mice receiving 1000 mg/kg of an ashwagandha root water extract,  $T_{max}$  for withaferin A and withanolide A were respectively 10 and 20 minutes. Another study using a different model suggests that ashwagandha is well absorbed after oral supplementation.

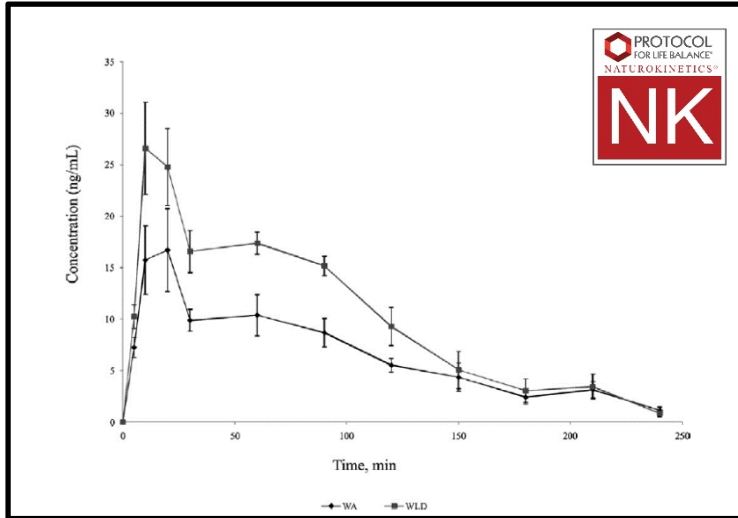


Figure 3: mean plasma concentration of withaferin A (WA) and withanolide A (WLD) after oral administration of *Withania somnifera* root aqueous extract at dose of 1000mg/kg in n=6 mice.

**Distribution:** The distribution of ashwagandha's bioactive compounds has not been evaluated. However, studies in animal models suggest that some of these bioactive compounds are able to pass the blood-brain barrier since physiologic changes are observed in the brains of animals ingesting ashwagandha extracts.

**Metabolism:** Information regarding ashwagandha's metabolism in the body is not yet available.

**Elimination:** Data from animal models suggest that the clearance from plasma is rapid.

## CLINICAL VALIDATION

- In a 12-week randomized, placebo-controlled clinical study on adult volunteers receiving Lactium® at a daily dose of 300 mg one hour before bedtime for four consecutive weeks, researchers observed in sleep diaries, a constant improvement in sleep efficiency in the

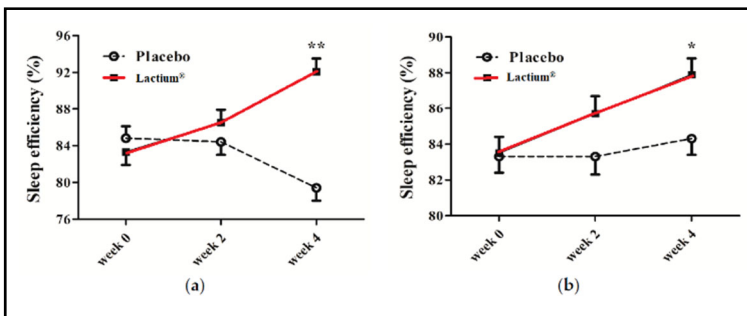
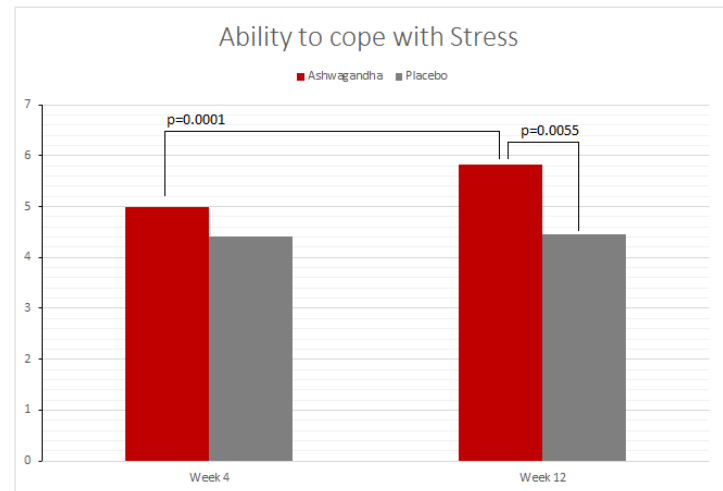


Figure 4: Comparison of effects of Lactium® administration on sleep efficiency. (a) Sleep diaries showed constant improvement in sleep efficiency for Lactium® group. Group difference in sleep efficiency over time became significant when Lactium® was administered for four weeks ( $p < 0.001$ ,  $q < 0.001$  for 0-4 weeks), (b) Actigraphy revealed a significant improvement after continuous use of Lactium® for four weeks ( $p = 0.007$ ,  $q = 0.016$  for 0-4 weeks). \*  $\alpha$ -value  $< 0.05$  and \*\*  $\alpha$ -value  $< 0.01$ . adapted from Kim *et al.*

Lactium® group. This improvement was confirmed after four weeks of supplementation by the measurement of sleep actigraphy.\*

- In a 30-day randomized, placebo-controlled clinical study on adult female volunteers receiving Lactium® at a daily dose of 150 mg, the authors observed a significant improvement in the subjective assessment of normal stress related symptoms, most notably on its impact on digestion ( $p < 0.01$ ), cardiovascular ( $p < 0.05$ ), intellectual ( $p < 0.01$ ), emotional ( $p < 0.05$ ) and social problems ( $p < 0.05$ ).\*
- In a 12-week randomized, placebo-controlled clinical study on adult volunteers receiving a standardized ashwagandha extract at a daily dose of 600 mg (300 mg twice daily), the authors observed a significant improvement in fatigue (assessed with a self-evaluation fatigue questionnaire) in the ashwagandha group compared to baseline and placebo.\* In this study, the ability to cope with stress was evaluated as a secondary endpoint using a 7-point visual analogue scale; volunteers in the ashwagandha group described a significant improvement in their ability to cope with stress versus baseline and versus placebo.\* Volunteers also showed improvements in their self-evaluation of quality of life (measured with SF-36 test).\*



## SAFETY INFORMATION

**Tolerability:** Lactium® is typically well tolerated in clinical studies.

Due to the presence of ashwagandha, this product may cause digestive upset in some sensitive individuals.

**Caution:** Thyroid function should be monitored at inception of supplementation with ashwagandha in individuals with a known thyroid function disorder.

**Contraindications:** This product is not recommended for individuals with known allergy/intolerance to bovine milk and milk products.

Due to the presence of ashwagandha, this product is not recommended for pregnant and nursing women.

## INTERACTIONS

**Drug Interactions:** Theoretically, Lactium® and ashwagandha may interfere with barbiturates and anxiolytics including benzodiazepines. Caution is recommended when combining these medications, Lactium® and

ashwagandha while driving or operating machinery. Ashwagandha may interfere with thyroid hormone medication; caution is advised.

**Supplement Interactions:** Theoretically, Lactium® and ashwagandha may potentiate supplements with sedative effects.

**Interaction with Lab Tests:** Some compounds found in ashwagandha may interfere with tests used to measure digoxin blood levels. This may result in falsely elevated digoxin levels - some test methods seem more affected than others.

Ashwagandha might interfere with thyroid function testing by decreasing TSH and increasing T3 and T4 values.

### **STORAGE**

Store at ambient conditions in tightly sealed container.