A Randomized, Triple-Blind, Placebo-Controlled Trial Investigating A Standardized Corn Leaf Extract On Sleep In Healthy Adults With Sleep Difficulties

Mesfin Yimam[1], Qi Jia[1], Katarina M. Doma[2], Abdelrahman Zamzam[2], David C. Crowley[2], Najla Guthrie[2], Erin D. Lewis[2]

[1]Unigen Inc., 2121 South State Street, Suite 400, Tacoma, WA 98405, USA

[2]KGK Science Inc., 275 Dundas Street, Tower A, Suite A1605, London, ON N6B 3L1, Canada

Abstract

INTRODUCTION: Difficulties falling and/or staying asleep affects over one quarter of American adults. Current management strategies include prescription sleep aids; however, long-term use is associated with adverse effects, and natural alternatives may provide safer and more effective relief. UP165, a standardized Corn Leaf Extract (CLE), has shown to bind melatonin receptors, increase melatonin synthesis and increase total sleep time (TST) and deep sleep in rodents and in a pilot clinical trial. Therefore, this study investigated the safety and efficacy of CLE on sleep quality in a healthy population.

METHODS: This clinical trial enrolled 80 healthy adults (18-65 years; n=40/group) with difficulties falling and/or staying asleep. Participants were assigned to CLE or placebo for 28 days. Following a 7-day run-in period, objective (actigraphy with electroencephalogram) and subjective (Pittsburgh Sleep Quality Index; PSQI) sleep measures, were assessed at baseline (Day 0), and Days 14 and 28, with safety assessed at screening and Day 28.

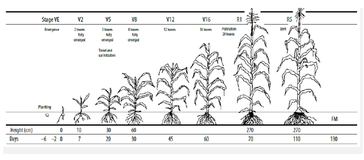
RESULTS: At Day 14, there was an increase in rapid eye movement (REM) (6.4 vs. -3.2 min; p=0.042) and decrease in awake duration (-17.9 vs. 17.0 min; p=0.021) for participants supplemented with CLE compared to those on placebo. At Day 28, there were increases in TST (35.2 vs. -16.9 min), REM (8.3 vs. -4.4 min) and light sleep time (30.8 vs. -12.4 min) for the CLE group compared to the placebo group ($p<0.05$). Compared to placebo, participants supplemented with CLE demonstrated significantly shorter sleep onset latency and less sleep fragmentation by Day 14. CLE improved sleep efficiency and increased sleep maintenance on both Days 14 and 28. The PSQI sleep latency score decreased from baseline at Days 14 and 28 for the CLE group, whereas the placebo group decreased at Day 28 only ($p<0.05$). Post-hoc analysis supported these findings with a significant increase of 35.7 min in non-REM sleep at Day 28 for participants supplemented with CLE compared to a decrease of 10.6 min for those on placebo. Supplementation with CLE was safe and well tolerated.

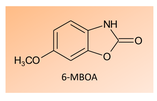
CONCLUSION: The current study suggests supplementation with CLE may improve sleep parameters in a healthy population with sleep difficulties.

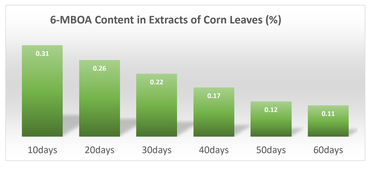
Corn Leaf Extract (CLE)

Corn Leaf Extract (CLE) is a standardized ethanol extract from Non-GMO corn (*Zea mays)* leaves harvested 20-25 days after germination. CLE contains 0.2% - 0.3% 6-Methoxy-2(3H)-benzoxazolone (6-MBOA) plus other nutritional components including 53% carbohydrates, 22% protein, 9% potassium, 6% fiber, and 1% Calcium. 6-MBOA is known to bind to melatonin receptors, stimulate melatonin synthesis, and upregulate expression of melatonin receptors.

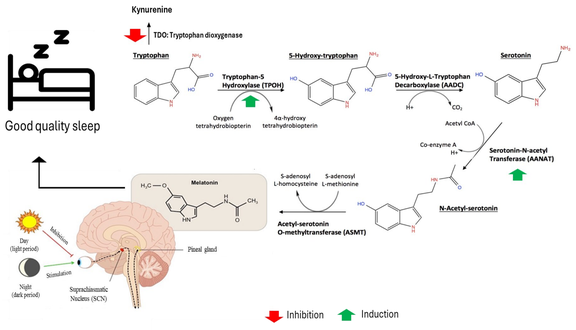
Corn Shoot Growth Process



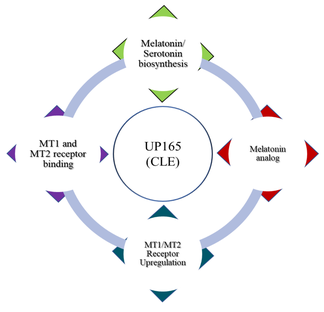


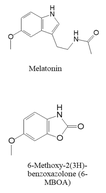


CLE Stimulates Synthesis of Serotonin & Melatonin

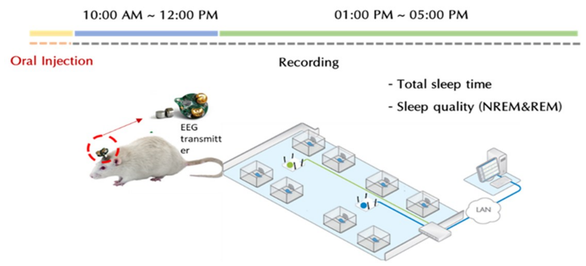


CLE Mechanisms of Action



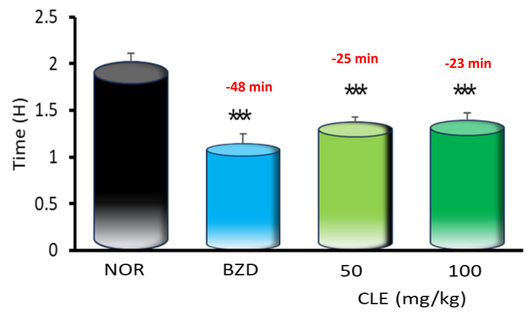


In vivo Proof of Concept Study Design

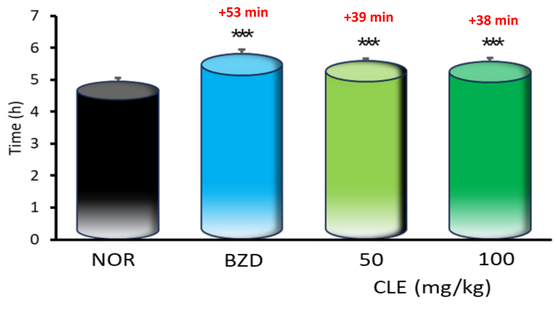


- **Transmitters were attached after a week of recovery from surgically installed electrodes**
- **Corn Leaf Extract (CLE) was administered orally at 50 and 100 mg/kg**
- **The reference compound, benzodiazepine (BZD), was given *i.p.*at 0.2 mg/kg**
- **Six rats were included per study group**
- **Study was run for 6 days and averages of these days were used for statistical analysis**

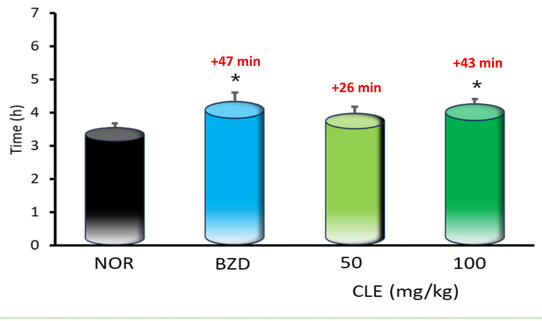
CLE Significantly Reduced Awake Time in Rats



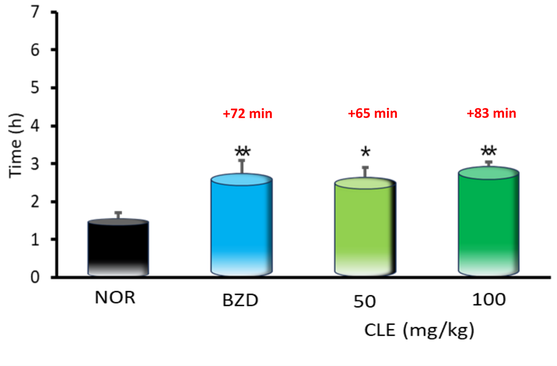
CLE Significantly Increased Total Sleep Time in Rats



CLE Significantly Increased NREM Sleep in Rats



CLE Significantly Increased Slow Wave Sleep in Rats



Randomized Triple-Blind, Placebo-Controlled Clinical Study

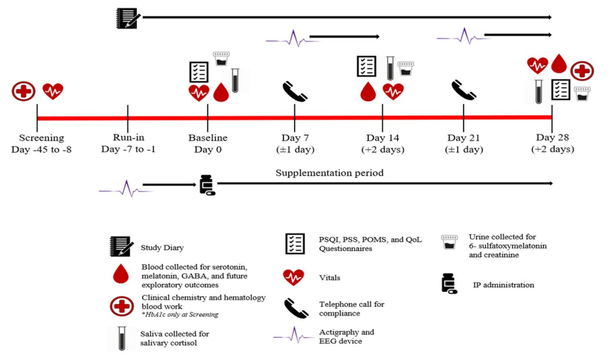
Consumed ~60 minutes prior to bedtime

CRO: KGK Science, LLC;
PI: David Crowley, M.D

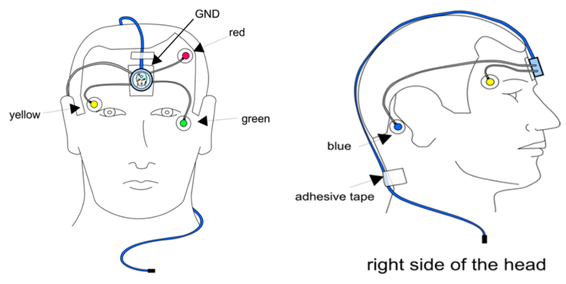
80 adults ages 18-65

- **Study design: A randomized, triple-blind, placebo-controlled, IRB-approved clinical trial**
- **Males (30%) and females (70%) between 18 and 65 years of age (average 46) , inclusive, at screening**
- **Recruited based on difficulty in falling asleep and/or staying asleep (normal, healthy subjects)**
- **Duration: 4 weeks**
- **Primary Endpoint measurements: TST, SL, SE, WASO, REM, NREM, number of awakenings >3 minutes as assessed by an EEG device**

Clinical Study Flow Chart

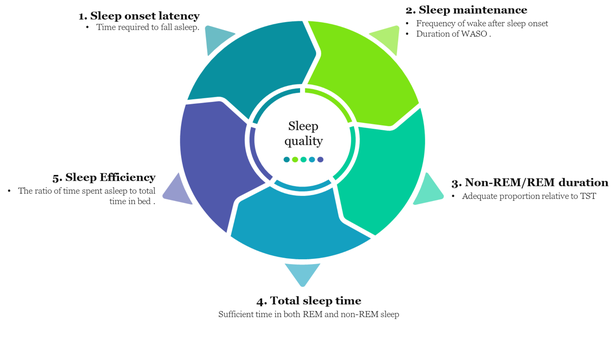


EEG Device and Electrode Placement

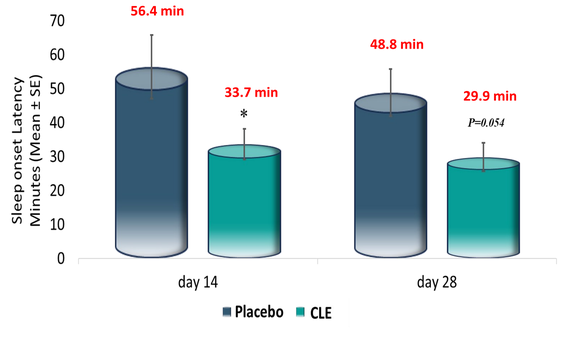


[SOMNOtouch™ RESP device, SN: TOR7258 (SOMNOmedics GmbH, Randersacker, Germany))

EEG Assessed Parameters

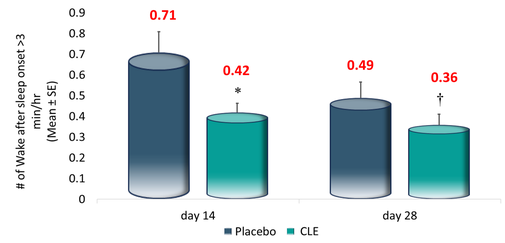


Corn Leaf Extract (CLE) Decreased Sleep Onset Latency



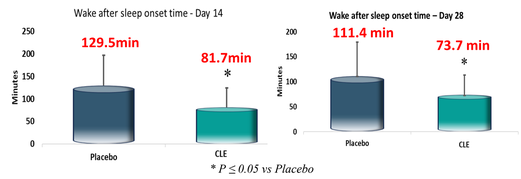
** P ≤ 0.05 vs Placebo*

CLE Decreased Sleep Disruption by 44%



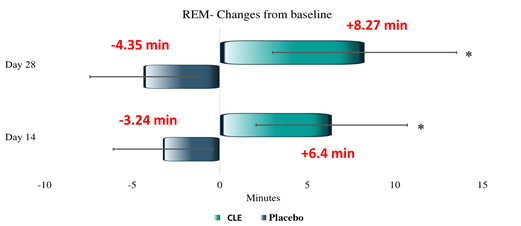
** P ≤ 0.05 vs Placebo † = P ≤ 0.05 vs baseline*

CLE Decreased Wake After Sleep Onset



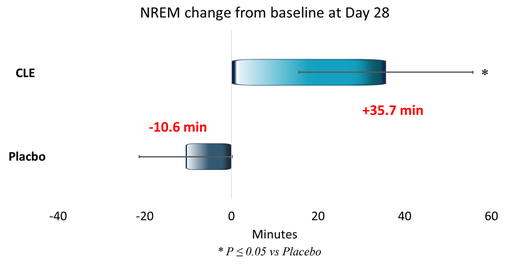
** P ≤ 0.05 vs Placebo*

CLE Increased REM Sleep Time



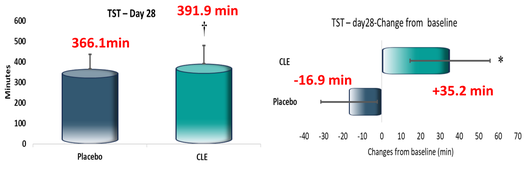
** P ≤ 0.05 vs Placebo*

CLE Increased NREM Sleep Time



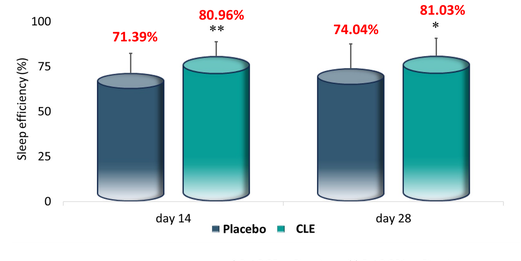
** P ≤ 0.05 vs Placebo*

CLE Increased Total Sleep Time



† = P ≤ 0.05 vs baseline ** P ≤ 0.05 vs Placebo*

CLE Increased Sleep Efficiency



** P ≤ 0.05 vs Placebo ** P ≤ 0.001 vs Placebo*

Summary

- **Corn Leaf Extract (CLE) was found to reduce sleep fragmentation by 44%**
- **CLE supported sleep maintenance by decreasing sleep disruption and reducing the awake time after initially falling sleep**
- **CLE group showed significantly increased REM and NREM sleep compared to placebo**
- **Duration of sleep was found increased for the CLE group compared to placebo**
- **CLE increased sleep efficiency compared to placebo**
- **CLE decreased sleep onset latency compared to placebo**
- **CLE resulted in perceived sleep quality improvement in PSQI from baseline**
- **CLE was found safe for human consumption**
- **Collectively, supplementation with Corn Leaf Extract (CLE) may improve sleep parameters in a healthy population with sleep difficulties**